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Epidemiology of blood component use in Finland

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ACADEMIC DISSERTATION

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II Palo R, Capraro L, Hovilehto S, Koivuranta M, Krusius T, Loponen E, Mäntykoski R, Pentti J, Pitkänen O, Raitakari M, Rimpiläinen J, Salmenperä M, Salo H, and Mäki T. Population-based audit of fresh-frozen plasma transfusion practices. Transfusion. 46;1921-1925:2006.

III Palo R, Ahonen J, Salo H, Salmenperä M, Krusius T, Mäki T. Transfusion of red blood cells: no impact on length of hospital stay in moderately anaemic parturients. Acta Anaesthesiologica Scandinavica. 51;565-569:2007.

IV Palo R, Capraro L, Hanhela R, Koivuranta M, Nikkinen L, Salmenperä M, Salonen I, Sjövall S, Tienhaara A, Vähämurto M, Mäki T. Platelet transfusions in adult patients with particular reference to patients undergoing surgery. Transfusion Medicine. 20; 30-37:2009.

V Palo R, Rinta-Kokko H, Nikkinen L, Salmenperä M, Mäki T. Correlation of ASA (American Society of Anesthesiologist) classification and blood transfusion requirement in surgical patients. (submitted)

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ABBREVIATIONS

aPTT	activated partial thromboplastin time
ASA	American Society of Anesthesiologists
CABG	coronary artery bypass grafting
DRG	diagnosis-related group
FFP	fresh frozen plasma
FHDR	Finnish Hospital Discharge Register
FRC BS	Finnish Red Cross Blood Service
Hb	hemoglobin
Hct	hematocrit
ICU	intensive care unit
INR	international normalized ratio
PLT	platelet
PT	prothrombin time
RBC	red blood cell
SAGM	sodium chloride-adenine-glucose-mannitol
SD	standard deviation
TRALI	transfusion-related lung injury
TURP	transurethral resection of the prostate
TTP	thrombotic thrombocytopenic purpura

ABSTRACT

Previously reported differences in transfusion practices suggest that transfusion protocols and clinical transfusion decisions may often be inappropriate. To change and monitor practices requires a follow-up system. A healthcare-integrated data-gathering system could provide the required information about blood use. The purpose of this observational study was to create a follow-up system for blood use and to gather information about transfused patients and transfusion practices in Finland.

Data came from ten Finnish hospital districts (five university and five tertiary-care hospital districts) between the years 2002 and 2005. The collection process involved combining data from electronic medical records applied for five different purposes: blood banking task-management, blood bank management, and laboratory test collection, as well as operating room purposes and a description of hospital visits. This information was combined from these electronic systems by use of personal identification numbers and data expressed as hospital episodes.

Validation of the combined data proved sufficient for study purposes. For example, 97% of adult blood products agreed with supplier's sales figures. Variation in blood-use practices still existed between hospitals. For example, the percentage of red blood cell (RBC) receivers ranged in Finnish hospitals from 12% to 57% during primary knee-arthroplasty surgery. Finnish blood recipients were generally elderly; over 50% of those transfused were over 65. The most typical blood-transfused patient was an over 65-year-old woman receiving 2 units of RBCs. About 10% of all blood products were transfused to children. RBC products and fresh frozen plasma (FFP) were usually transfused in pairs (such as in two-four-six units). Most (over 60%) of the transfused FFP went to surgical patients. One-fourth of FFP-transfused surgery patients suffered from blood circulatory system diseases. In over 30% of FFP transfusions, plasma was given without any guidance from coagulation tests. In Finland, about 100 FFP units and 400 RBC units were transfused during 1 000 hospital visits including surgery. Among moderately anemic parturients, transfusion of 0 to 2 units of RBC had no effect on length of hospitalization. Duration of hospitalization was, however, considerably longer in these anemic patients than for average Finnish mothers (5.2 days versus 3.5 days). Most of the platelet (PLT) products were transfused to hematological patients (43%). Only 1% of surgical patients received PLTs. Most of the PLT-transfused patients were surgical (54%). PLT recipients undergoing surgery had higher in-hospital mortality rates (13.1%) than did PLT-transfused patients overall (9.5%). Severity of underlying condition as judged by the American Society of Anesthesiologists' Physical Status (ASA) Classification in surgical patients had an effect on prevalence of blood

transfusions. For example, patients classified to ASA grade 3 or 4 received almost 70% of all transfused blood products. Severity of disease was used in our study to predict RBC need in hip-arthroplasty patients.

Variability in blood-use practices suggests inappropriate blood use. Moreover, RBC transfusion in paired units is a questionable practice. FFP transfusions, not based on coagulation tests, suggest inappropriate use of plasma as well. In parturients, mild anemia treated with 1 to 2 units of RBCs does not shorten hospitalization time. This supports the current recommended thresholds for RBC transfusion. Improvement efforts concerning PLT-use practices may be directed to users of high doses of PLTs; to hematological patients, but also to digestive tract surgery and cardiac surgery patients who receive a large amount of transfused PLTs. Knowledge of severity of the underlying disease as affecting the transfusion requirement may facilitate optimization of blood use.

INTRODUCTION

Blood transfusion has been an important part of medical treatment since World War II. Blood-component treatment can be lifesaving in many situations, but blood administration has physiological and immunological effects that can be harmful or can hamper later transfusions. Annually in Finland, approximately 200 to 300 harmful reactions from blood transfusion are reported to the Finnish Red Cross Blood Service (FRC BS) (Adverse effects of blood transfusion 2010, 2011). Some 20 to 40 of these are considered serious.

The most common serious hazard of transfusion is the administration of a blood component intended for another patient (Adverse effects of blood transfusion 2010, 2011). Transfusions can cause adverse effects (anaphylaxis, transfusion-related lung injury: TRALI), and infections can be transmitted via blood (human immunodeficiency virus, hepatitis, prion diseases) (Schreiber et al., 1996; Sandler, Vassallo, 2001; Kleinman et al., 2004; Lefrère, Hewitt, 2009). Furthermore, duration of RBC storage is associated with an increase in adverse outcomes (Spinella et al., 2009; Pettilä et al., 2011). True transfusion reactions and infectious problems are, fortunately, rare. However, unnecessary blood transfusions expose patients needlessly to potential risks from transfusions.

Blood collection and preparation are costly. In 2010, Finnish hospitals spent over 45 million euros to purchase blood components from the FRC BS (The Blood Service in 2010, 2010). No information exists as to Finnish hospitals' laboratory, personnel, supplies, and additional costs associated with blood transfusions, but studies from several countries suggest that, from a larger, societal perspective, blood component use costs are much higher and increasing (Cremieux et al., 2000; Varney et al., 2003; Amin et al., 2004; Glenngård et al., 2005). All this justifies the conclusion that unnecessary blood transfusions produce redundant healthcare costs.

Aging of the population strains the supply chain of blood components. One estimate is that in the United Kingdom within 20 years, use of blood products will increase by 20% compared to the supply (Currie et al., 2004). The number of eligible blood donors might become insufficient in the near future.

Practically no information exists as to the current epidemiology of blood transfusions in Finland. Studies on blood use show, however, great variation between hospitals and countries (Sirchia et al., 1994; Kytölä et al., 1998; Capraro et al., 1998, 2000). Variation has been thought primarily to reflect differences in clinical transfusion practices. Up to several-fold differences in the percentage of transfused patients or in the number of transfused blood components indicate that blood use cannot always be optimal. Knowledge of current blood use indications does not coincide with clinical practice, or it just

might be scanty. Commonly accepted and applied guidelines or working methods might facilitate everyday clinical work and more importantly, improve patient care.

To improve blood use practices, the need for current epidemiology is acknowledged. Most effectively, continuous follow-up of blood use would be accomplished by a healthcare integrated information system. It would offer the possibility for administrators and clinical personnel performing transfusions to monitor hospitals' individual blood use and to compare practices between hospitals (i.e. benchmarking). Furthermore, it could provide a data foundation for interventions to change transfusion practices.

For this study we developed a permanent national registry of blood component use utilizing electronic hospital information systems. We studied epidemiology of blood component use and Finnish blood use practices. Furthermore, in specific groups, particular issues related to transfusions were chosen and examined more close, like indications for blood transfusions, correlation between blood transfusions and length of hospital stay, and in-hospital mortality. The aim of the present study was to provide tools for transfusion practice improvement by providing information about blood use and by suggesting clinically useful measures for the advancement of blood-use practices.

REVIEW OF THE LITERATURE

1. Epidemiology of blood component use

Epidemiological information on blood component use is limited. Most information has concentrated on certain blood components, diagnoses, or surgical procedures, on particular areas or hospitals, and has restricted the data gathered by time limits, thus lacking follow-up on changing practices. Furthermore, data collection requiring manual manpower has proven laborious. Only a few studies extend these limits (Sirchia et al., 1994; Mathoulin-Pelissier et al., 2000; Titlestad et al., 2001, 2002; Wells et al., 2002; Snyder-Ramos et al., 2008; Kamper-Jørgensen et al., 2009). The Sanguis study compared blood component use practices in 43 teaching hospitals in 10 European countries for six commonly performed elective surgical procedures (Sirchia et al., 1994). Titlestad et al. (2001, 2002) used computerized registries to study transfused patients. RECEPT investigators searched transfusion-related variables based on a random sampling method to study 3,206 transfused patients in 175 hospitals across France, and Wells et al. (2002) conducted a study based on hospital blood-bank information in northern England for a population of 2.9 million (Mathoulin-Pelissier et al., 2000). Snyder-Ramos et al. (2008) studied 5,065 randomly selected cardiac surgery patients in 70 centers among 16 countries in North and South America, Europe, the Middle East, and Asia. A Danish-Swedish group combined transfusion information in order to study population-based blood transfusion exposure (Kamper-Jørjensen et al., 2009).

1.1. Clinical use of red blood cells

According to several studies, roughly half of all RBC units are used for surgical indications and the other half for other medical indications (Friedman et al., 1980, 1982; Cook and Epps, 1991; Ghali et al., 1994; Vamvakas and Taswell, 1994; Chiavetta et al., 1996; Beguin et al., 1998; Stanworth et al., 2002; Wells et al., 2002; Wallis et al., 2006; Barr et al., 2010). RBC-transfused patients are generally elderly. About half of all RBC recipients are aged 65 years or more (Wells et al., 2002, 2009; Cobain et al., 2007; Barr et al., 2010; Borkent-Raven et al., 2010; Bosch et al., 2011). More women are transfused with RBCs than men, but men are transfused with more RBC units than are women, on average (Vamvakas and Taswell, 1994; Zimmermann et al., 1997, 1998; Wells et al., 2002, 2009; Anderson et al., 2007; Cobain et al., 2007; Menis et al., 2009; Barr et al., 2010; Borkent-Raven et al., 2010; Madren et al., 2010; Bosch et al., 2011). Most of the RBCs are transfused to patients with malignancies or gastrointestinal or cardiovascular diseases, or to trauma patients (Chiavetta et

al., 1996; Zimmermann et al., 1997, 1998; Mathoulin-Pelissier et al., 2000; Lim et al., 2004; Cobain et al., 2007; Wells et al., 2009; Barr et al., 2010; Borkent-Raven et al., 2010; Madsen et al., 2010; Bosch et al., 2011). Major RBC recipients are patients with coronary heart disease as their recorded main diagnosis (Chiavetta et al., 1996; Titlestad et al., 2001; Anderson et al., 2007; Menis et al., 2009; Bosch et al., 2011). In the perioperative setting, RBCs are transfused most often to orthopedic and cardiac or vascular surgery patients (Chiavetta et al., 1996; Stanworth et al., 2002; Wells et al., 2002; Anderson et al., 2007). The majority of surgically treated RBC receivers undergo abdominal surgery, coronary artery bypass (CABG), or hip replacement. Study details of previous RBC use research are in the appendix.

Cardiac surgery and red blood cell transfusion

Cardiac surgery remains one of the major consumers of allogeneic blood (Society of Thoracic Surgeons Blood Conservation Guideline Task Force, 2011). Vascular surgery and use of cardiopulmonary bypass expose these patients to major bleeding, so CABG patients represent the single largest group of blood recipients (Surgenor et al., 1992). Goodnough et al. (1991) estimated that in the U.S. CABG patients comprise nearly 10% of annual RBC recipients. They found in their 18-institution study of 540 elective CABG patients that 68% of the patients received RBCs. Surgenor et al. (1992) reported at the same time that isolated CABG patients (including primary and re-do operations) received a mean 4.3 to 6.7 units of RBCs depending on type of procedure. RBC transfusion frequency (71-85%) also varied between operation types. Variation is evident in CABG patients' RBC transfusion frequencies, ranging from 0 to 100% (Sirchia et al., 1994; Hasley et al., 1995; Stover et al., 1998, 2000; Snyder-Ramos et al., 2008; Mehta et al., 2009). A study in Finnish hospitals found 87% (range 53-99%) of first-time, elective CABG-operated patients receiving RBCs (Kytölä et al., 1998). Reported figures from Japan (74%) and the U.S. (34%) have been lower (Isomatsu et al., 2001; Covin et al., 2003). However, according to The Society of Thoracic Surgeons Blood Conservation Guideline Task Force (2007), more than half of all cardiac patients do not receive blood products; of blood units transfused, a minority (15-20%) of operated cardiac patients consume most: 80%. A restricted program of RBC use is possible, since of 441 consecutive CABG patients of one surgeon, only 10% received RBCs (mean 0.3±1.4 units) (Cosgrove et al., 1985).

Abdominal aortic surgery patients and red blood cell transfusion

Vascular surgical procedures are often accompanied by excessive bleeding. When Hallett et al. (1987) studied the effect of an autotransfusion device in elective abdominal aortic surgery, they found 96% of elective abdominal aortic surgery patients to require allogeneic blood (RBCs or whole blood). Use of autotransfusion reduced the percentage of allogenic transfusion recipients to

32%. Sirchia et al. (1994) found the frequency of transfused abdominal aorta aneurysmectomy patients to vary markedly among 43 hospitals (mean 53.7%, range 7-100%). When Long et al. (2010) studied retrospectively open abdominal aortic aneurysm repair patients and compared RBC transfusion practices between 1980 to 1982 and 2003 to 2006 in the Mayo Clinic, they found a statistically significant decrease in intraoperatively RBC-transfused patients in the latter observation period (99% vs. 46%).

Hip' and knee-replacement patients and red blood cell transfusion

Orthopedic surgery is associated with major perioperative blood loss. Most orthopedic blood recipients studied are total hip- and knee-replacement patients. Surgenor et al. (1991) investigated 4,315 primary hip' or knee-replacement patients and found large variation in RBC requirements (hip: 54-87% transfused; knee: 33-78% transfused). Hasley et al. (1995) studied 7,173 patients undergoing hip' or knee-replacement. They found 69% (range 36-95%; mean units 2.6, SD 1.4) of hip' and 51% (9-97%; mean units 2.2, SD 0.9) of knee-replacement patients to receive RBCs. The percentage of RBC recipients among hip-replacement patients was lower (57%, range 0-100%, median of units 3, range 2-5) in the Sanguis study with 1,647 patients (Sirchia et al., 1994). In Finland, Capraro (1998) found 92% (mean units 3.6, SD 2.3) of primary unilateral total hip' and 84% (mean units 2.6, SD 2.0) of knee-replacement patients to need allogeneic RBCs during 1992-1994. The percentage of allogeneic RBC recipients in these elective orthopedic procedures has ranged from 10 to 35% depending on autotransfusion regimen in three large studies from Europe and the U.S. (Bierbaum et al., 1999; Borghi et al., 2000; Rosencher et al., 2003).

Feagan's group (2001) studied 2,032 consecutive patients undergoing hip-and knee replacements and the effect of autologous blood donation on their blood requirement. They found the percentage of allogeneic RBC receivers in primary hip replacement to be 30% (7% in the autologous blood-donation group) and in the primary knee replacement procedure 17% (7% in the autologous blood donation group). The mean number of allogeneic RBC units transfused were a respective 2.3 (1.7) and 2.3 (3.0). Utilizing patient-related indicators when ordering RBCs for total hip arthroplasty reduced the amount of crossmatched RBCs by 61% and the efficiency of blood-ordering practices rose (Nuttall et al., 1996, 1998).

Femoral-neck fracture patients and red blood cell transfusion

Fracture of the femoral neck is associated with bleeding and need for transfusions (Friedman et al., 1980; Wells et al., 2002). Swain et al. (2000) studied their operated and non-operated femoral-neck fracture patients and found 53% to have been transfused with a mean of 2.6 units of RBCs. This percentage of transfused and operated hip-fracture patients has shown a

variability between 24 and 61% in three studies from the U.S. and Canada (Goodnough et al., 1993; Poses et al., 1998; Hutton et al., 2005). Johnston et al. (2006) reported an allogeneic blood transfusion rate of 30% in their operated hip-fracture patients with no association between transfusion and mortality rate. The surgical technique chosen has been shown to influence RBC requirements in hip-fracture patients, with replacement arthroplasty patients needing more blood transfusions than did patients treated with internal fixation (Parker and Gurusamy, 2006; Parker and Handoll, 2006). Hutton et al. (2005) showed variability in mean nadir Hb counts after adjustment for age and gender following hip-fracture repair. Mean Hb counts ranged between Canadian hospitals from 71.2±2.9 g/l to 82.8±1.7 g/l (mean 77.6±11.6 g/l).

Gastrointestinal bleeding and red blood cell transfusion

Hematemesis and melena are the major signs of gastrointestinal bleeding most often caused by ulcers, varices, or gastrointestinal tumors. Coagulopathy caused by liver dysfunction occurs commonly in these patients and is associated with massive hemorrhage. The A/S/G/E Bleeding Survey, conducted in 1978 and 1979 (Gilbert, 1990), was a prospective study comprising 2,225 patients with upper gastrointestinal bleeding. They found 26% of patients each requiring more than 5 units of RBCs (median 3.6 units). A study of 4,664 gastric and duodenal ulcer patients found an RBC transfusion frequency of 50% (range 11-76% between hospitals) (Hasley et al., 1995). One 7-year retrospective study of patients with gastrointestinal bleeding showed patients with portal hypertension (90% were transfused) and with gastric (69%) and duodenal ulcers (53% required RBC transfusion) to require most of the transfused RBC units (Garrido et al., 2006). Advances in endoscopic methods and novel pharmacologic approaches have reduced the need for transfusions in patients with upper gastrointestinal bleeding. Hospitalization of these patients has shown a decrease. Re-bleeding for variceal patients decreased from 10% in 1991 to 6% in 2000 and for non-variceal patients from 8% in 1997 to 6% in 2000 (Lee et al., 2005).

Colorectal resection for cancer and red blood cell transfusion

High rates of perioperative blood transfusion ranging from 20% to 70% have been reported for patients undergoing colorectal resection for cancer (Francis et al., 1987; Weiden et al., 1987; Tang et al., 1993; Donohue et al., 1995; Chiarugi et al., 1996; Edna and Bjerkeset, 1998; Vamvakas and Carven, 1998; Benoists et al., 2001; Skånberg et al., 2007). In one 14,052 colorectal-surgery data-set, only 19% of patients received transfusions (allogeneic or autologous RBCs, FFP, or PLTs) (Nilsson et al., 2002). A decreased transfusion requirement is associated with greater operation volume/surgeon per year and also with a hospital's lower annual patient volume. Rate of RBC transfusion in colorectal surgery was almost the same, 20%, in a study by Kim et al. (2007). Choosing

laparoscopy-assisted surgery instead of conventional open surgery reduces the percentage of patients transfused (Ohtani et al., 2011).

Trauma patients and red blood cell transfusion

Trauma is a major cause for bleeding, and about 10 to 15% of all transfused RBCs go to trauma patients (Friedman et al., 1980). Wudel et al. (1991) studied massively transfused blunt-trauma patients in the U.S.; a total of 6,142 patients were admitted for trauma in their level I-trauma center, when patients with penetrating trauma or burns were excluded. They found 92 of these patients had received transfusion of 20 or more RBC units, totaling 3,004 units of RBCs. Como et al. (2004) reported that of 5,645 acute-trauma patients, 8% received RBCs. Of these 5,645 injured individuals, 147 (3%) received more than 10 units, and they were transfused with 71% of all RBCs given. Mc Roberts et al. (2007) confirmed the finding of a minority of injured patients receiving the greatest volume of blood products. A post hoc analysis of the CRIT study in the U.S. showed that 55% of trauma patients in intensive care units received RBCs (Shapiro et al., 2003). Of 120 trauma patients expected to remain in the surgical intensive care unit (ICU) for longer than 48 hours, 87% (104) received RBCs (Beale et al., 2006). In a nationwide benchmarking study from the U.S., 15% of trauma patients requiring ICU care received RBCs (Lilly et al., 2011).

Intensive care patients and red blood cell transfusion

In intensive care patients, anemia is very common. Epidemiological studies in the 1990s found 30 to 85% of ICU patients receiving RBCs (Corwin et al., 1995; Littenberg et al., 1995; Borum et al., 2000), and during this same time-period, Groeger et al. (1993) found 27% of patients in surgical ICUs and 16% in medical ICUs as being transfused with RBCs. RBC transfusion practices seem to have changed little over the decade. Vincent et al. (2002) studied 3,534 patients admitted to 146 western European ICUs in the ABC trial. Transfusion rate during their ICU stay was 37%, and the mean number of transfused RBC units was 4.8 (SD 5.2). Mean age of the patients was 61 (SD 17), with the majority being males (62%). Emergency surgery patients were transfused with RBCs most often (57%), followed by trauma patients (48%), elective surgery patients (42%), and other medical patients (32%).

Corwin et al. (1995), in a prospective, multi-center, observational CRIT study of 248 ICUs in the U.S. with 4,892 patients, found that 44% of critically ill patients received RBCs (mean 4.6, SD 4.9 units). In these large, prospective studies from Europe and the U.S., mean pretransfusion Hb was 84 (SD 13 g/l) and 86g/l (SD 17 g/l), respectively (Vincent et al., 2002; Corwin et al., 2004). Rao et al. (2002) studied transfusion frequencies in nine ICUs in the U.K., where 53% of ICU patients received RBCs. Hemorrhage patients received on average 6.75 units of RBCs and anemia patients 4.25 units. Over half (91 of 176) of one teaching hospital's ICU patients received RBCs (Chohan et al., 2003).

These findings differ widely from those of an Australian study in a university-associated tertiary hospital in which only 23% of intensive care patients were transfused (Farrar et al., 2004), and from the ATIC study group's in 10 ICUs in Scotland where 40% of ICU admissions were associated with RBC transfusion (Walsh et. al., 2004). A recent benchmarking study including 243,533 adult ICU admissions in the U.S. reported 19% of patients as receiving RBCs (Lilly et al., 2011).

Obstetric and gynecological patients and red blood cell transfusion

Obstetric hemorrhage remains a major cause for maternal mortality (Khan et al., 2006; Knight et al., 2009). Unfortunately, most deaths involve substandard care, so there may be room for improvement of transfusion procedures (Bonnet et al., 2011). Otherwise obstetric and other gynecological patients require blood transfusions relatively infrequently. This patient population accounts for 2 to 6% of all RBC use, with variation between studies (Chiavetta et al., 1996; Stanworth et al., 2002; Wells et al., 2002).

Cesarean section and hysterectomy are the two surgical procedures performed most often. Transfusions are necessary in 0.3 to 3% of vaginal and in 0.7 to 12% of cesarean deliveries (Hill and Lavin, 1983; Andres et al., 1990; Klapholz, 1990; Dickason and Dinsmoor, 1992; Goudan et al., 2011). A number of hysterectomy patients are also transfused, and as many as 17 to 75% of these patients reportedly receive RBCs (Mintz and Sullivan, 1985; Palmer et al., 1986). A more recent study by Kohli et al. (2000) reported a 3.4% incidence of blood transfusion among elective hysterectomy patients and noticed that routine Hb monitoring after surgery in asymptomatic women did not improve outcome. Bleeding complications necessitating blood transfusion perioperatively were in one study more common in vaginal hysterectomies than in abdominal procedures for benign diseases in Finland (Mäkinen et al., 2001), but this finding disagrees with Turkish researchers' retrospective findings that vaginal hysterectomy patients less frequently received blood (Doganay et al., 2011). The incidence of transfusion was low in both studies (vaginal hysterectomy: 3% vs. 2%, abdominal hysterectomy: 2% vs. almost 3%).

Dosing of red blood cells

Several studies from Denmark, the U.S., Australia, Austria, and the Netherlands show that RBC units are transfused most often in paired doses (Titlestad et al., 2001; Shapiro et al., 2003; Grey et al., 2006; Gombotz et al., 2007; Borkent-Raven et al., 2010). Routine paired dosing of RBCs can be seen in various specialities (Grey et al., 2006).

1.2. Clinical use of fresh frozen plasma

Two-thirds of FFP units are transfused to surgical patients (Cook and Epps, 1991; Iorio et al., 2008). Most FFP recipients are male, and the majority of FFP

units go to male patients (Vamvakas and Taswell, 1994; Zimmermann et al., 1997, 1998; Cobain et al., 2007; Iorio et al., 2008; Mirzamani et al., 2009; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011). The majority of FFP recipients are elderly, with 40 to 50% of FFP units transfused to patients over 65 (Zimmermann et al., 1998; Cobain et al., 2007; Iorio et al., 2008; Mirzamani et al., 2009; Wells et al., 2009; Borkent-Raven et al., 2010; Stanworth et al., 2011). FFP recipients are, however, younger on average than RBC recipients (Cook and Epps, 1991; Tynell et al., 2001; Cobain et al., 2007; Borkent-Raven et al., 2010). The majority of FFP recipients have a gastrointestinal or circulatory system disease, malignancy, or trauma (Zimmermann et al., 1997, 1998; Mathoulin-Pelissier et al., 2000; Lim et al., 2004; Cobain et al., 2007; Mirzamani et al., 2009; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011). The most frequent diagnosis associated with FFP transfusion is coronary artery disease (Titlestad et al., 2001; Bosch et al., 2011). Study details of previous FFP use research are shown in the appendix.

Digestive system diseases and FFP transfusion

Patients with gastrointestinal disease require FFP transfusion for the same indications as with RBCs (ulcers and varices), and the most common abnormality seen with gastrointestinal bleeding is the coagulopathy of liver disease. Reports are fewer on the FFP requirement in gastrointestinal patients than on RBC transfusions. However, a survey from the USA on gastrointestinal bleeding caused by varices found 45% of these patients to require FFP transfusions during their first bleeding episode (median 3 units) (Sorbi et al., 2003). The FFP transfusion rate was higher during re-bleeding (51%). In 2007, 24% of all transfused FFP units in Catalonian hospitals were for patients with gastrointestinal disease (Bocsh et al., 2011).

Cardiovascular disease and FFP transfusion

Up to 50% of FFP units are transfused to patients with cardiovascular disease (Zimmermann et al., 1997; Cobain et al., 2007; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011). The Sanguis study group found 39% (range 0-100%) of European CABG patients being transfused with FFP at a median of four units each (range 1-10) (Sirchia et al., 1994). A later study from the USA, including 18 institutions, found 32% (range 0-97%) of first-time, elective CABG patients receiving FFP (Goodnough et al., 1991). Moreover, a study of nine centers in Finland showed that 25% (range 5-49%; mean number of transfused units 2.8, SD 1.9) of these patients received FFP transfusions (Kytölä et al., 1998). Stover et al. (1998) also found a high variability in FFP transfusion practices, 0 to 36% of CABG patients being transfused with FFP. However, the percentage of FFP-transfused patients in the USA reported by Covin et al. (2003) was lower, 9% (range 0-10%). Snyder-Ramos et al. (2008)

also found variability in FFP transfusion practices in patients undergoing CABG among 70 centers in 16 countries in North and South America, Europe, the Middle East, and Asia. FFP transfusion frequencies ranged from 0 to 98% intraoperatively, and from 3 to 95% postoperatively.

Intensive care patients and FFP transfusion
Patients with major bleeding often require ICU care. FFP has been transfused to 23% of patients admitted to an ICU, and 32% of FFP-transfused patients have been in an ICU (Rao et al., 2002; Stanworth et al., 2011). Lilly et al. in 2011, reported, however, only 5% of ICU patients in the USA as receiving FFP in a study including 243,533 adult patient admissions in 271 ICUs located in 188 hospitals. Dara et al. (2005) found 38% of ICU patients with a prolonged international normalized ratio (INR; INR≥1.5) without active bleeding as receiving FFP. The majority of FFP is transfused for prophylactic reasons (Dara et al., 2005; Stanworth et al., 2011).

Dosing of FFP
In Denmark and the Netherlands, FFP units are administered in pairs, as are RBCs (Titlestad et al., 2001; Borkent-Raven et al. 2010). No explanation for this practice, except as a custom of medical personnel, has emerged (Titlestad et al., 2001).

1.3. Clinical use of platelets

Over half of all PLT recipients in the USA are surgical patients (Cook and Epps, 1991). About two-thirds of PLT-transfused patients are male, and they receive roughly 60% of transfused PLTs (Vamvakas and Taswell, 1994; Zimmermann et al., 1997, 1998; Cobain et al., 2007; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011). PLT-transfused patients are on average younger than are RBC and FFP recipients (Cobain et al., 2007; Greeno et al., 2007; Borkent-Raven et al., 2010). Most PLTs are transfused to patients with a malignancy (Zimmermann et al., 1997; Mathoulin-Pelissier et al., 2000; Titlestad et al., 2001; Lim et al., 2004; Cobain et al., 2007; Greeno et al., 2007; Quareshi et al., 2007; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011). Study details of earlier PLT use research are in as appendix.

Hematological patients and PLT transfusion
Prophylactic PLT transfusions are often given to reduce risk for hemorrhage in patients undergoing chemotherapy for cancer. Most PLT-transfused cancer patients have a hematological malignancy, and patients with acute leukemia and bone marrow transplants receive most of the PLT transfusions (Bayer et al., 1992; Zimmermann et al., 1997; Meehan et al., 2000; Titlestad et al., 2001). Cameron et al. (2007) reported at their referral hospital that 67% of PLT transfusions went to hematological patients, most (78%) being for prophylaxis.

Cardiac surgery and PLT transfusion

Cardiac surgery patients often receive PLTs perioperatively. Use of cardiopulmonary bypass has an effect on the number and function of PLTs. Of the Goodnoughs et al. (1991) first-time, elective CABG-operated patients in the USA, 22% (range 0-80%) received PLTs, whereas Kytölä et al. (1998) found a rate in Finland of only 9% (range 2-22%; mean of transfused units 8.3; SD 3.6). Stover et al. (1998) found that the percentage of PLT-transfused CABG patients in the USA differed between hospitals, ranging between 0 and 36%. In a more recent study from the USA, Covin et al. (2003) found the percentage to be 10% (range 4.8-18.4%). Snyder-Ramos et al. (2008) found their percentage of CABG PLT-transfused patients to be 17% (mean of transfused units 6.9) in an international comparative study.

Intensive care patients and PLT transfusion

Rao et al. (2002) studied critically ill patients in the U.K. and found 16% of ICU patients to receive PLT transfusions. Most patients (44%) received PLTs with a transfusion trigger of a PLT count between 50 and $100x10^9$/L. Arnold et al. (2006) found 23% of adult ICU patients who were expected to stay in an ICU for at least 72 hours (excluding trauma-, orthopedic- and cardiac-surgery patients) as receiving PLT transfusions. PLT transfusion triggers (median) for prophylactic PLT transfusion were $41x10^9$/L and for therapeutic purposes higher, $51x10^9$/L. Lilly et al. (2011) found in their benchmarking study from the USA that only 3% of adult ICU patients received PLTs.

1.4. Use of blood components by diagnosis-related groups

One way of approaching blood-component use is to analyze the cost of transfusion care. Originally developed for reimbursement and for a description of hospital activity, diagnosis-related groups (DRG) have been utilized for study of transfused patients. The DRG classification is based on the idea that similar patients require similar resources during any one treatment episode. Cook and Epps (1991) found that 74% of transfused patients, 74% of transfusion episodes, and 76% of transfused blood components (RBC, FFP, and PLT) were transfused to patients in 5 of the 18 major DRGs: 1. cardiovascular (24% of RBC units and 34% of FFP units), 2. neoplasm (26% of PLT units), 3. digestive, 4. injury/poisoning, and 5. musculoskeletal diagnoses. Jefferies LC et al. (2001) studied in 1995 the transfusion costs in 60 hospitals and found the DRGs: 1. bone marrow transplantation, 2. liver transplantation and 3. acute leukemia (without major operating room procedure: age over 17 years), to induce the highest blood costs.

In 1998 Syrjälä et al. (2001) found in one Finnish university-hospital setting the highest blood component costs in DRG groups: in acute leukemia (without major

operating room procedure: age>17 years), in bone marrow transplantation, and in lymphoma or non-acute leukemia without complications. A recent study from Australia found that patients receiving most of the transfused RBCs either had a tracheostomy or were patients ventilated for over 95 hours, patients with RBC disorder without catastrophic or severe comorbidities, and patients with lymphoma and non-acute leukemia (Allden et al., 2011). Surgenor et al. (1989, 1991, 1992, 1998) and Vamvakas (1998) also utilized DRG groups to study transfusion practices.

1.5. Variation in blood-use practices

Variation in blood-component usage has been well documented (Surgenor et al., 1989; Goodnough et al., 1991; Baele et al., 1994; Sirchia et al., 1994; Hasley et al., 1995; Audet et al., 1998; Capraro et al., 1998; Kytölä et al., 1998; Stover et al., 1998; Surgenor et al., 1998; Hebert et al., 1999; Feagan et al., 2001; Vincent et al., 2002; Rosencher et al., 2003; Hutton et al., 2005; Gombozt et al., 2007; Snyder-Ramos et al., 2008). Variation has occurred within specific disease categories and surgical procedures, within clinical settings and between institutions. The Sanguis group study of 1994 found the percentage of transfused elective surgery patients in 43 European countries to range among hospitals from 0 to 100%. Hebert et al. (1999) found the mean pretransfusion Hb to range in Canadian ICU patients from 87 g/l to 95 g/l, and Hutton et al. (2005) observed nadir Hb to range from 67 g/l to 85 g/l in various surgical and critical care patient groups. Transfusion rates depend on patient population, on differences in perioperative blood loss, and on the treating physicians. Many authors have concluded that variation in blood use practices suggests inappropriate use of blood components.

2. Optimal use of blood components

Few randomized, controlled trials concern the clinical use of blood components, and the majority of guidelines are based on clinical experience and professional consensus (Table 1).

Table 1. *Guidelines for use of blood components.*

Guidelines	Guidelines for use of red blood cells	Guidelines for use of fresh frozen plasma	Guidelines for use of platelets
Task Force of College of American Pathologists, 1994		yes	
Task Force of College of American Pathologists, 1995		yes	
Crosby et al., 1997	yes	yes	
Ancliff and Marchin, 1998			yes
Council NHMR, 2001	yes	yes	yes
Murphy et al., 2001	yes		
Schiffer et al., 2001			yes
Agence Française de Sécurité des Produits de Santé, 2002		yes	
British Committee for Standards in Haematology, 2003			yes
O'Shaughnessy et al., 2004		yes	
Stanworth et al, 2004			yes
Stanworth et al, 2005			yes
American Society of Anesthesiologists Task Force, 2006	yes		
Samama et al., 2006			yes
Breivik et al., 2010			yes

2.1. Guidelines for use of red blood cells

In the past, clinicians have used the 100/30 transfusion rule as a transfusion trigger to keep patients' Hb concentrations above 100 g/l and hematocrits (Hct) above 30%. Over the years, the scientific foundation for this trigger to transfuse RBCs has been challenged.

RBCs are transfused depending on patient's clinical condition, ability to tolerate anemia, and bleeding status. Recommendations exist for clinicians regarding Hb thresholds to trigger RBC transfusion, but no optimal strategy has been defined for treatment of a particular single patient (Crosby et al., 1997; Council NHAMR, 2001; Murphy et al., 2001; American Society of Anesthesiologists Task Force, 2006). For most non-bleeding patients, RBC transfusion is probably unnecessary until the Hb value drops below 70 g/l, with the exception of patients with severe coronary disease (Hebert et al., 1999, 2001; Carless et al., 2010). These patients probably require higher Hb levels to ensure adequate oxygen delivery to the cardiac muscle. Furthermore, patients with acute blood loss of 30 to 40% of blood volume most probably need RBC transfusions (Murphy et al., 2001). Moreover, massively bleeding patients benefit from a higher Hb target due to the acute nature of the bleeding, and because Hct as high as 35% may be required to sustain hemostasis (Blajchman et al., 1994; Hardy et al., 2004,

2005). The possibility to monitor the patient (blood pressure, heart rate, electrocardiography, cardiac index, mixed venous oxygen saturation) helps to assess the adequacy of perfusion and oxygenation of vital organs (American Society of Anesthesiologists Task Force, 2006).

Randomized, controlled data to support these guidelines come from a small number of studies including mainly adult patients. Current evidence on clinical outcome on the subject of transfusion thresholds appears in a Cochrane metanalysis by Carless et al. (2010). They found altogether 17 randomized, controlled studies comparing clinical outcomes in patients randomized to restrictive or liberal transfusion thresholds over a time period exceeding 40 years (Fisher and Topley, 1956; Blair et al, 1986: Fortune et al., 1987; Johnson et al., 1992; Hebert et al., 1995; Bush et al., 1997; Carson et al., 1998; Bracey et al., 1999; Hebert et al., 1999; Lotke et al, 1999; Grover et al., 2006; Lacroix et al., 2007; Colomo et al., 2008; Webert et al., 2008; Foss et al., 2009; Zygun et al., 2009; So-Osman et al., 2010). This metanalysis found that published evidence suggests no effect of conservative transfusion triggers on mortality, on rates of cardiac events, morbidity, or length of hospitalization. Especially if safety of the blood supply is in doubt, minimizing transfusions can be favorable. An even more recent randomized study enrolling hip-fracture surgery patients concluded that a liberal transfusion strategy reduced neither mortality nor patients' ability to walk independently on the 60th-day control visit (Carson et al., 2011). This agrees with earlier findings (Carson et al., 1998).

Children's optimal threshold for RBC transfusion has been evaluated in randomized studies. A Canadian research team studied stable, critically ill children treated in an ICU (Lacroix et al., 2007). They assigned 320 patients to an Hb trigger group at 70 g/l, and 317 patients to a group at 95 g/l. The restrictive transfusion strategy was as safe as a liberal one. A metanalysis for extremely low birth weight infants (under 1,500 g) found no statistically significant differences in serious morbidity or death between babies in restrictive and liberal transfusion threshold groups (Kirpalani et al., 2006; Chen et al., 2009; Whyte et al., 2009; Nopoulos et al., 2011; Whyte and Kirpalani, 2011). Infants' respiratory status (intubated or not intubated) and age influenced the targeted transfusion threshold values in these very small babies.

2.2. Guidelines for use of fresh frozen plasma

FFP transfusion is indicated in patients with a single coagulation factor deficiency when no virus-safe fractionated product is available, and for blood loss in patients with multiple coagulation factor deficiencies or disseminated intravascular coagulation (Crosby et. al., 1997; Council NHAMR, 2001; Agence Francaise de Securite des Produits de Sante, 2002; O'Shaugnessy et al., 2004). Furthermore, FFP is indicated in reversal of the warfarin effect in bleeding

patients, plasma exchange in thrombotic thrombocytopenic purpura (TTP), and prevention of bleeding in patients with liver diseases and prolonged protrombin time. Recent randomized evidence emphasizes the therapeutic use of FFP and use of coagulation tests to guide decision-making (O'Shaugnessy et al., 2004; Stanworth et al., 2004). Contraindications for FFP use are treatment for hypovolemia, for plasma exchange (except for TTP), for reversal of prolonged INR in the absence of bleeding, and when prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT) are normal (O'Shaugnessy et al., 2004; American Society of Anesthesiologists, 2006). Coagulation parameter thresholds triggering FFP transfusion in case of bleeding are presence of a PT greater than 1.5 times normal or INR greater than 2.0, an aPTT greater than 1.5 to 2 times normal, or a fibrinogen level under 100 mg/dL (Task Force of College of American Pathologists, 1994; Crosby et. al., 1997; Council NHAMR, 2001; Agence Francaise de Securite des Produits de Sante, 2002; O'Shaugnessy et al., 2004; American Society of Anesthesiologist, 2006). FFP dosage depends on the FFP product, clinical situation, and on coagulation monitoring availability. In Finland a starting dose of 10 to 15 ml/kg is the recommendation of the FRC BS, the supplier (Mäki ed., 2004).

In support of currently recommended practice guidelines, randomized, controlled-study evidence on the effectiveness of FFP is limited (Murad et al, 2010; Roback et al., 2010). Most randomized trials have been underpowered or lacked blinding. Furthermore, in the absence of randomized, controlled data on FFP transfusion-triggering laboratory values, clinical use of FFP becomes challenging. However, some randomized evidence exists. Rock et al., (1991) compared plasma exchange with plasma infusion in 102 TTP patients. They found improved rates of response and survival in their plasma-exchange group. The Northern Neonatal Nursing Initiative Trial Group compared FFP with volume expanders in preventing intraventricular hemorrhage in 518 neonates (The NNNI Trial Group, 1996). They found no effect from prophylactic use of FFP. Leese et al., (1987) studied 198 adult patients with acute pancreatitis, randomizing patients to receive either FFP or a colloid solution. No differences emerged between groups as to clinical or laboratory outcomes. More data are clearly needed (Wood et al., 2009).

2.3. Guidelines for use of platelets

Recent guidelines recommend prophylactic PLT transfusion for stable patients with cancer or a blood disorder when the patient's PLT count falls below $10x10^9$/L (Ancliff and Marchin, 1998; Council NHAMR, 2001: Schiffer et al., 2001; British Committee for Standards in Haematology, 2003; Stanworth et al., 2004). Patients are recommended to be monitored carefully for signs and symptoms of increased risk for bleeding (including elevated body temperature, rapid decrease in PLT count, and sepsis) and the transfusion threshold requires

raising if appropriate. An ongoing international study evaluates the concept of prophylactic PLT use (Stanworth et al., 2010). In surgical patients, the threshold for prophylactic PLT transfusion is higher than in conservatively treated patients. For commonly practiced invasive procedures, a PLT count of 50 $x10^9$/L is adequate, with higher thresholds recommended for patients undergoing neurosurgery or ophthalmic surgery (100 $x10^9$/L), and for those having epidural anesthesia (80 $x10^9$/L) (Council NHAMR, 2001; Samama et al., 2006). Nordic guidelines for neuraxial blocks take into account the potential benefit of the block (Breivik et al., 2010). The PLT transfusion threshold recommended decreases when the benefit of block treatment improves. Prophylactic PLT transfusion is not recommended for patients on PLT inhibitor therapy. Furthermore, surgery-related guidelines emphasize documenting any PLT deficit with test results (British Committee for Standards in Haematology, 2003; American Society of Anesthesiologists Task Force, 2006; Samama et al., 2006). PLT dosage relates to each individual clinical situation. With acute massive bleeding, the suggested dose is 1 unit per 10 kg of body weight (Mäki ed., 2004).

Stanworth et al. (2004) reviewed randomized, controlled studies involving prophylactic PLT transfusions after chemotherapy and stem cell transplantation in patients with hematological malignancies. These included eight published trials (Roy et al., 1973; Higby et al., 1974; Solomon et al., 1978; Murphy et al., 1982; Sintnicolaas et al., 1982; Heckman et al., 1997; Rebulla et al., 1997; Klumpp et al., 1999; Zumberg et al., 2002). Four of these studies took place 20 to 30 years ago under conditions differing from those for current treatment. Metanalysis found no evidence to change current practice regarding recommendation of a prophylactic threshold of $10x10^9$/L. Later, Diedrich et al. (2005) compared 166 allogeneic hematopoietic progenitor cell transplant recipients randomly assigned to receive PLTs with a transfusion trigger of less than $10x10^9$/L or less than $30x10^9$/L. They concluded that both thresholds were safe. For prophylaxis, the number of transfused PLTs has had no effect on incidence of bleeding in hematological patients (Slichter et al., 2010); they compared 1,272 patients receiving either low-, medium-, or high-dose PLTs per square meter of body-surface area.

Most of the recommendations in the perioperative setting are based solely on expert opinion. Two small (60 and 28 patients), randomized studies on cardiopulmonary bypass patients showed that prophylactic PLT transfusions are ineffective. Studies suggest that PLTs are reserved for patients bleeding after cardiopulmonary bypass, when surgical causes for bleeding have been excluded (Harding et al., 1975; Simon al., 1984).

3. Use of electronic information in hospital databanks

3.1. Finnish Hospital Discharge Register (FHDR)

In Finland, information on hospital visits has been collected in the FHDR since 1967 (Gissler and Haukka, 2004). From the mid 1980's, hospitals have been sending this information in electronic form. Later, from the early 90's, other databases and programs for different hospital functions (for example, electronic blood bank systems) have become common and more uniform, and the trend towards replacing all printed patient charts by computerized medical registers is nationwide (Koskimies, 1999). Information on FHDR was designed to serve healthcare planning purposes. Such data have been widely useful for research, but also for comparison of hospital practice and care improvement (for example in productivity of hospitals, in care for the elderly, in dental care) (Gissler and Haukka, 2004; Hospital benchmarking, 2005; Helin-Salmivaara et al., 2006; Winell et al., 2006). The quality of FHDR data has been good (Keskimäki and Aro, 1991; Kantonen et al., 1997; Pajunen et al., 2005; Mattila et al., 2008).

3.2. Electronic information and transfusion research

Electronic data have been sporadically used to study transfusion practices (Syrjälä et al., 2001; Titlestad et al, 2002; McClelland, 2007; Grey et al., 2006; Borkent-Raven et al., 2010). Information from electronic databanks designed for various purposes was combined in these studies and served for research.

Transfusion-related electronic data have been gathered on a larger scale in Scandinavia. The Danish Transfusion Database was founded in 1997 to study Danish blood-component use practices (Dansk Transfusionsdatabase, home page on the Internet). The Danish database includes transfusion-related information on patient diagnosis, treatment, blood transfusions, and clinical/chemical parameters. Existing electronic registers and information systems gather this regularly updated transfusion data, and reporting has been mandatory for all Danish hospitals since 2006. Analysis of these data are published and accessible on the Danish Healthcare Services health portal on the Internet.

The largest database including transfusion-related data in electronic form is the SCANDAT database. It was designed to study cancer incidence in blood donors and transfusion recipients and to investigate the possibility that cancer can be transmitted via blood transfusion (Edgren et al., 2006). The database comprises over 10 million blood donations and transfusions in Sweden and Denmark between 1968 and 2002 (SCANDAT, home page on the Internet). The blood

donation and transfusion data gathered from hospital blood bank databases was linked with the cause of death, hospital inpatient, and birth and cancer registers from both countries. Plans are to update it.

4. Trends in blood component use

4.1. Red blood cell usage

The FRC BSs´yearly sales figures show a decreasing trend in RBC use in Finland (Figure 1, provided by Tom Krusius, medical director, FRC BS). Finland is one of the European countries in which RBCs are used quite liberally (Figure 2) (Council of Europe, 2001-2008).

Figure 1. *Red blood cell and whole blood units provided by the Finnish Red Cross Transfusion Service to Finnish hospitals, 1984-2011.*

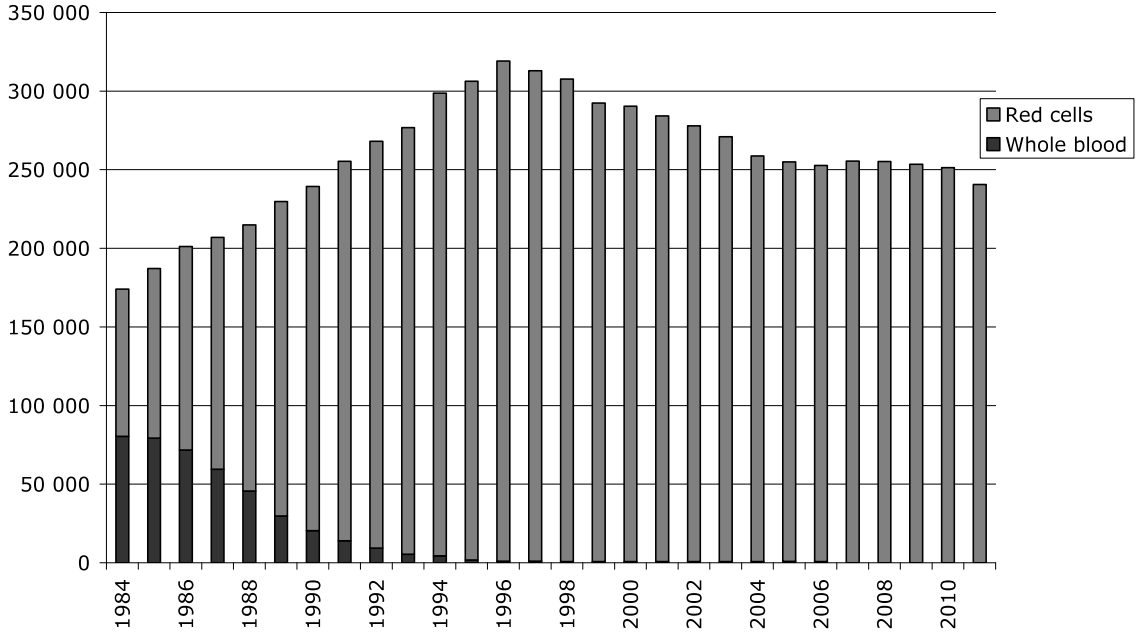
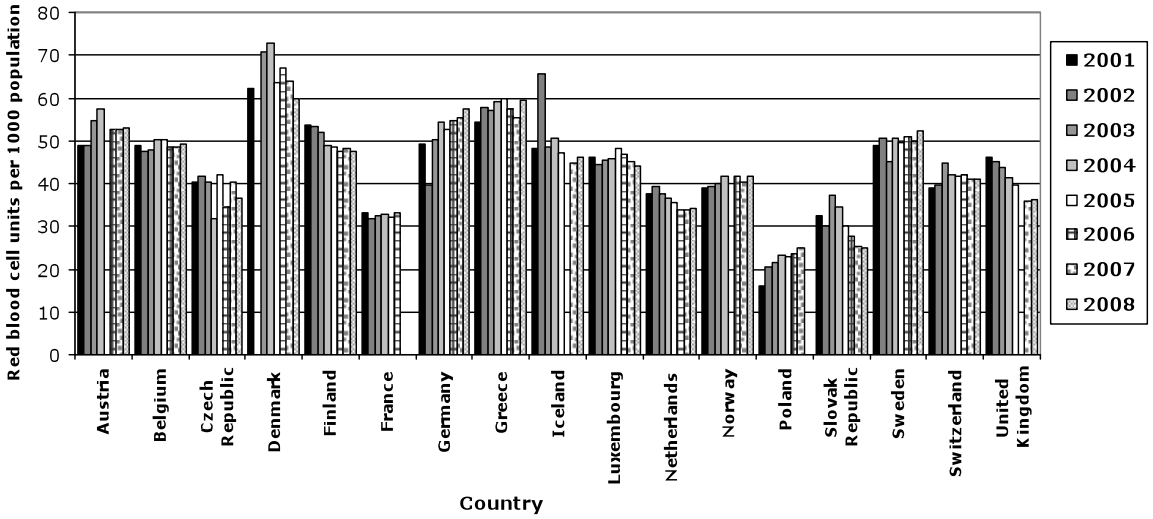


Figure 2. *Red blood cell use per 1,000 population in European countries 2001-2008 provided by the Council of Europe.*



4.4. Fresh frozen plasma usage

Although indications for administration of FFP have tightened over the years, plasma transfusions are given more and more often (Figure 3, FRC BS sales figures provided by Tom Krusius, medical director, FRC BS; O'Shaugnessy et al., 2004). Differing from the liberal usage of RBCs in Finland, Finnish FFP use seems to rank at the average international level (Figure 4) (Council of Europe, 2001-2008). The Finnish FFP/RBC use ratio per 1,000 population is one of the lowest internationally (Figure 5) (Council of Europe, 2001-2008). In the USA the rising trend for FFP use resembles Finnish figures (Sullivan et al., 2007; National Blood Collection and Utilization Survey Report, 2009; Figure 3). The significant rise in FFP use seen in FRC BS sales figures is in part explained by the change in fresh frozen plasma product (Figure 3). The FFP product used previously comprised on average more coagulation factors per ml, and the size of the product was larger than was Octaplas®.

Figure 3. *Fresh frozen plasma units provided in 1984-2011 by the Finnish Red Cross Transfusion Service and Octapharma to Finnish hospitals.*

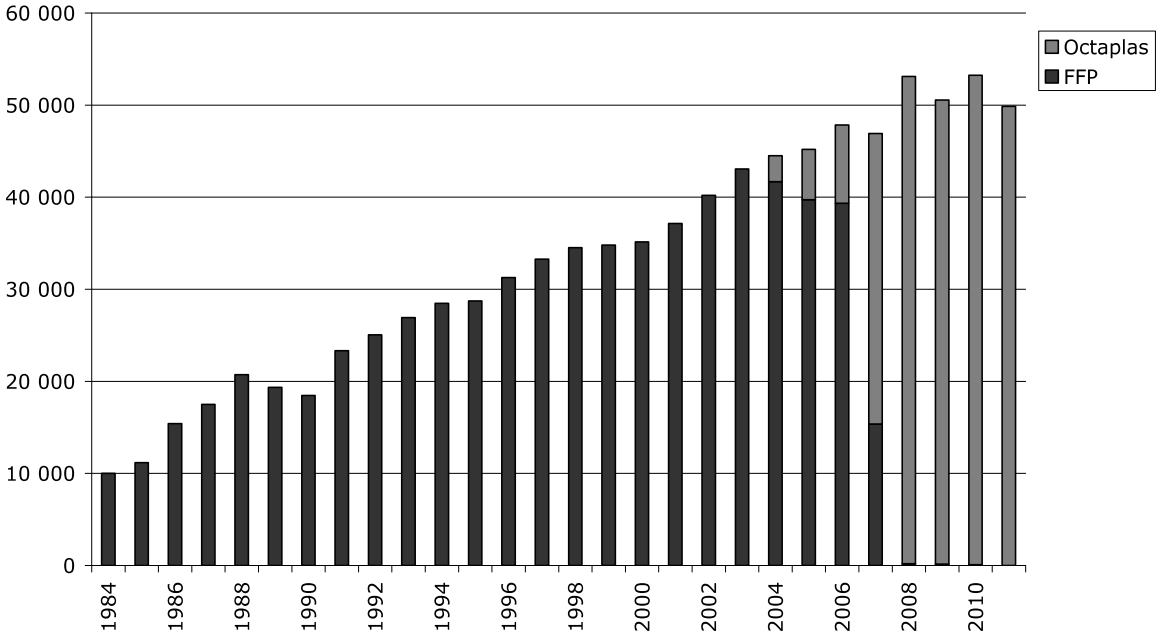


Figure 4*. Fresh frozen plasma use per 1,000 population in European countries 2001-2008 provided by the Council of Europe.*

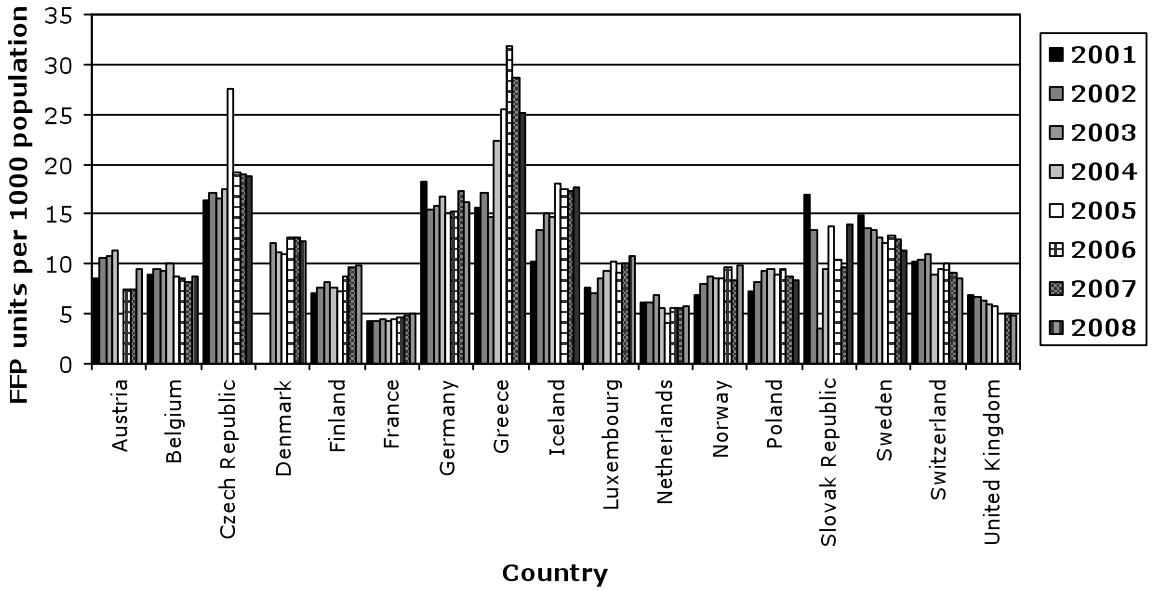
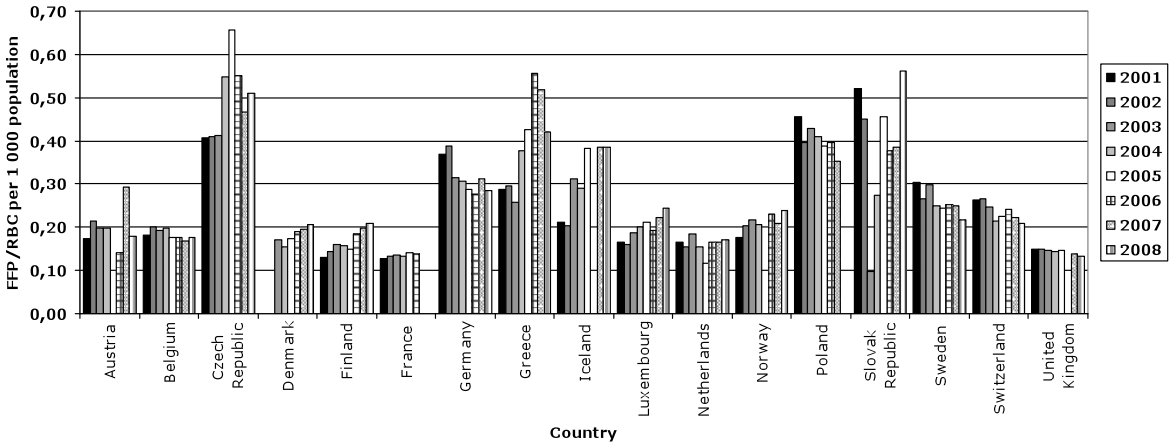


Figure 5. *Fresh frozen plasma use per red blood cell use per 1,000 population in European countries 2001-2008 provided by the Council of Europe.*



4.4. Platelet usage

The FRC BSs overall PLT sales trend seems to be toward an increase (Figure 6, FRC BS sales figures provided by Tom Krusius, medical director, FRC BS). The recent PLT use trend in Europe seems to be more stable than trends for other blood products (Figure 7) (Council of Europe, 2001-2005). In the USA, PLT use is increasing, in agreement with FRC BS sales figures (Sullivan et al., 2007; National Blood Collection and Utilization Survey Report, 2009; Figure 6).

***Figure 6**. Platelet product use in Finnish hospitals 1984-2011. Each product equals 4 units.*

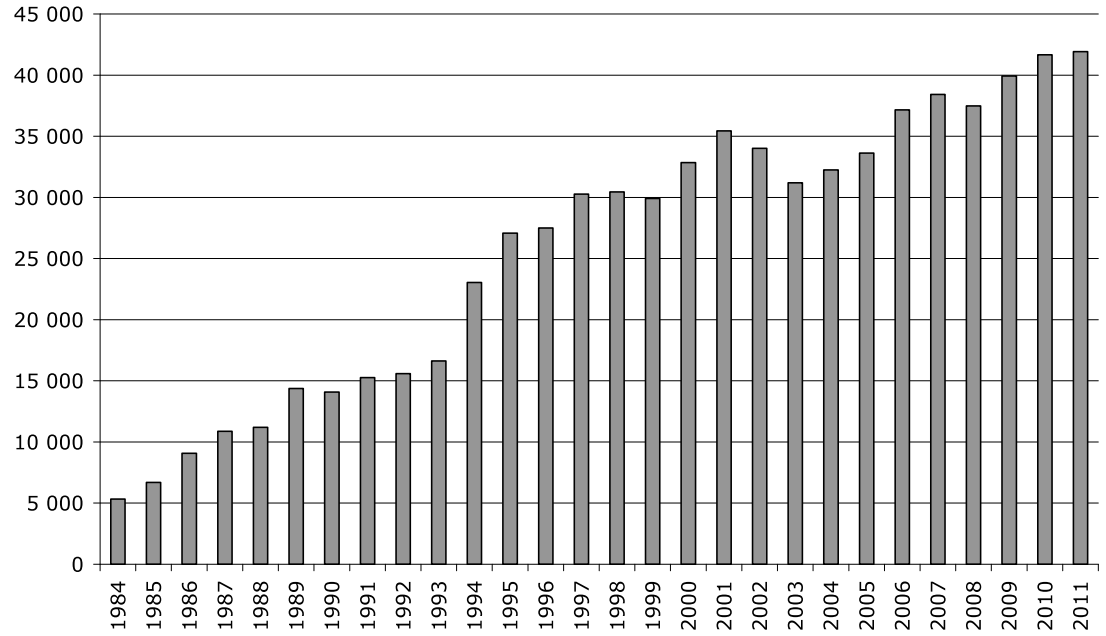
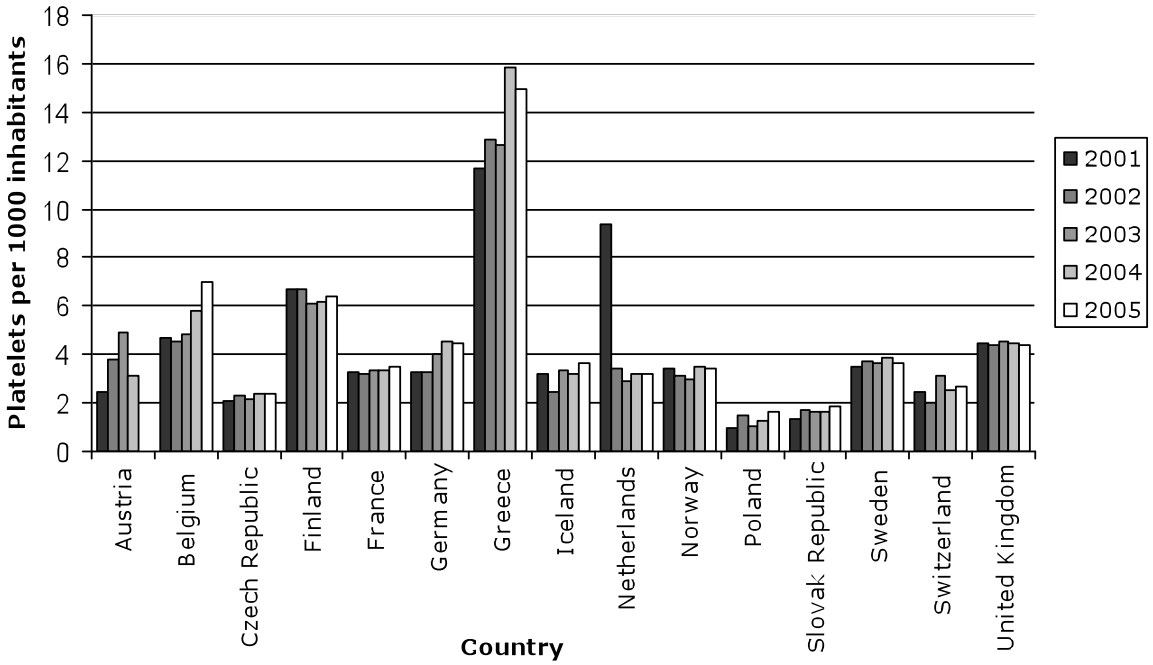


***Figure 7.** Platelet use per 1000 inhabitants in European countries in 2001-2005 provided by the Council of Europe.*



4.4. Future trends in blood component use and costs

The population structure in most Western countries is shifting from younger to older age groups. In Finland, the proportion of individuals aged over 65 is predicted to increase from 17% to 29% between 2009 and 2060 (Suomen virallinen tilasto, 2009). Aging leads to increased risk for disease and need for transfusions (Wells et al., 2002, 2009; Cobain et al., 2007; Akif et al., 2010; Barr et al., 2010; Borkent-Raven et al., 2010; Bosch et al., 2011). The eligible donor group will be smaller in an aging population, and concern has arisen as to the sufficiency of the future blood supply (Currie et al., 2003; Borkent-Raven et al., 2010; Katalinic et al., 2010; Greinacher et al., 2011). Variables such as optimizing blood component use may counterbalance the predicted need for transfusions (Borkent-Raven et al., 2010).

Increased demand for blood components raises the cost of transfusion therapy. In addition, improving product safety (screening for infectious agents, leukoreduction, solvent/detergent treatment) or other increasing annual expenses involving collection, preparation and distribution raise the cost for blood products paid by the hospitals (Table 3). Blood product processing by the hospital transfusion services, blood administration to patients, wastage of blood, transfusion-reaction management, opportunity cost of donor's time all influence the overall costs of transfusions (Amin et al., 2004; Glenngård et al., 2005). Resources are, however, limited, and cost-effectiveness analysis can help rational decision-making in focusing future improvements in blood safety (Custer and Hoch, 2009).

AIMS OF THE STUDY

The general aim of this observational study was to develop and establish a data-gathering system for studying the epidemiology of blood transfusions in Finland (I) and to examine and compare transfusion practices in Finnish hospitals (II, III, IV, V).

The specific aims were:

1. To describe blood component (RBC, FFP, and PLT)-transfused patients in Finland and to compare transfusion practices in common elective surgical procedures between hospitals (I).

2. To study FFP use and FFP transfusion practices in Finland, and to compare Finnish and international data (II).

3. To determine the impact of RBC transfusions on hospitalization length in moderately anemic parturients (III).

4. To describe the population of PLT-transfused patients in Finland, in particular those PLT recipients undergoing surgery (IV).

5. To study the association between blood transfusion and ASA classification in surgical patients (V).

MATERIALS AND METHODS

1. Finnish healthcare system and blood transfusion service

Primary healthcare in Finland is organized by approximately 270 health centers providing outpatient medical care, inpatient care, and preventive services by doctors, mainly general practitioners, nurses and other medical professionals (Ministry of Social Affairs and Health, 2004). Inpatients treated in health center wards are usually elderly and chronically ill.

Secondary healthcare is provided by 5 university hospital districts and 16 central hospital districts. Finland's hospital districts include, besides university or central hospitals, also 40 other smaller specialized hospitals (i.e. district hospitals). Secondary healthcare services include inpatient and outpatient medical care by specialized doctors, nurses, and other healthcare professionals.

Privately provided healthcare services consist mainly of outpatient care, and only a few private hospitals are available in Finland's largest cities.

The FRC BS is a non-profit, independently functioning unit of the Finnish Red Cross. It collects and produces blood and plasma products from blood that is donated entirely voluntarily, with no payment to the donors, who are Finnish residents. The Blood Service was Finland's only blood-component supplier from 1996 to 2003. In 2004, an FRC BS collaboration with Octapharma made it possible also to purchase solvent detergent FFP (Octaplas®) in Finland.

2. Participants

At the end of 2002, three university hospital districts and the FRC BS began a project for benchmarking and improving blood use practices in Finland (Mäki, 2007). The aim was to create a national information system regarding transfused patients. Eight Finnish hospital districts joined from the beginning and two districts later. Hospital districts participated on a voluntary basis, with the expenses of creating the data system divided between participants and the FRC BS. Written informed consent was not required for observational and anonymous data registration. Steering group members appointed by the participating hospital districts approved the study.

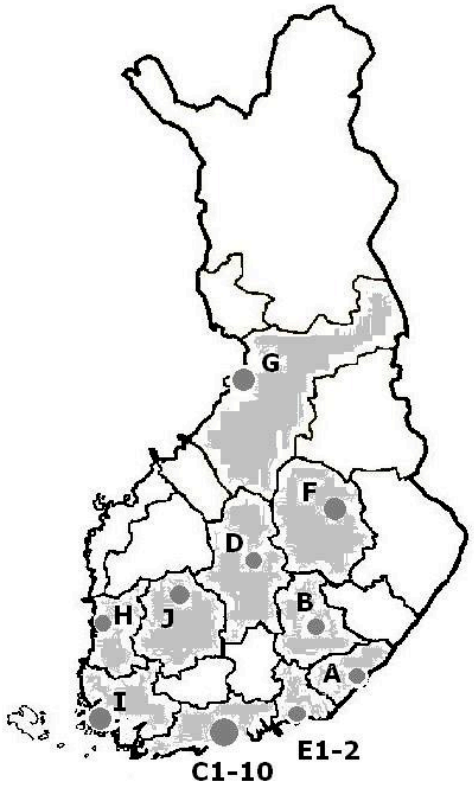
In 2002 and 2003 nine Finnish hospital districts participated in our study. Four of them were university-hospital-led (C, F, G, I) and five were central-hospital-connected (A, B, D, E, H). Participating hospitals were located in the most heavily populated regions in Finland (Figure 8). Annually, these hospital districts

have about 620,000 inpatient episodes, constituting 63% of all inpatient visits provided by the Finnish secondary healthcare system.

In 2004 and 2005, participants comprised four university hospital districts (C, F, G, J) and five central-hospital-connected districts (A, B, D, E, H). They manage about 64% of annual inpatient episodes. Due to the conversion by hospital I to an updated hospital administration system and because hospital district J joined later, their participants differed slightly from those in the 2002-2003 study period.

Hospital districts C and E included several separately managed hospitals and therefore we reported these hospitals independently. In Finland, treatment of some special patients is centralized in university hospitals, this including organ transplantation, pediatric open-heart surgery, major burn injuries, allogenic bone-marrow transplantation, and acute leukemia.

Figure 8. *Participating hospitals and hospital districts, 2002-2005.*



3. Data collection

Data were collected from hospitals, which fulfilled all technical requirements and could deliver all necessary data. In practice, hospitals were required to have a transfusion database, and included were all major transfusing hospitals.

Personal identification numbers were chosen for all patients transfused or potentially at transfusion risk: 1. patients for whom blood components (RBC, FFP, or PLT) were ordered (these patients were not necessarily transfused), 2. all surgical patients with procedure codes (NCSP, the NOMESCO Classification of Surgical Procedures, classification of surgical procedure, 2003) starting with A, B, C, D, E, F, G, H, J, K, L, M, N, P, Q, and Y, omitting patients with small or merely diagnostic procedures (i.e. codes starting with T, U, X and Z) and 3. patients with their main diagnoses as ICD-10, International Classification of Disease, 10th revision, 1999 C81-C96, D45-D47, D50-D77, O00-O99.8, P50-P61, S00-S99.9, T00-T07, T20-T23, T79-T98, and Z99.9. These diagnoses included patients with malignant disorders, anemia of any cause, obstetric disorders, fetal or neonatal hemorrhagic and hematological disorders, and burns or trauma. Collected personal identification numbers included, besides transfused patients, also patients to serve as controls for further use (for example, all obstetric patients).

All data recorded under selected personal identification numbers were gathered from these hospitals' pre-existing information registers. These systems were designed for administrative purposes (Musti, Tietoenator Oyj, Espoo, Finland; SAPO, OYS, Oulu, Finland), laboratory tasks (MultiLab, Mylab Oy, Tampere, Finland; OYSlab, OYS, Oulu, Finland), operating room responsibilities (ToTi, WM-Data Novo Oyj, Espoo, Finland; LESU, OYS, Oulu, Finland; Musti, Tietoenator Oyj, Espoo, Finland), and hospital blood center work (Vertti, MyLab Oy, Tampere, Finland; OYSlab, OYS, Oulu, Finland). All data recorded in the FRC BS blood banking task program (Progesa; MAK-SYSTEM, Paris, France) were also included for quality verification purposes.

Patients´ personal identification numbers were encrypted by a coding computer program (DWcrypt, Datawell Oy, Espoo, Finland). This coding program used a different password for each hospital district. This security measure ensured that a patient treated in two hospital districts had two different database identification numbers, ensuring anonymity. Passwords were entrusted to only one person from each hospital district to guarantee anonymity.

Personal identification numbers and time stamps in the data assisted in pre-processing and assembling all information gathered into hospital episodes. The final hospital episode comprised one patient visit to one medical specialty. Pre-processing and assembling of the program (VOK pre-processing, Datawell Oy, Espoo, Finland) combined 90 originally collected transfusion-related variables into 149 parameters to describe each episode (Optimal use of blood components, 2006). The main groups of variables were patient demographics (gender, age), place of treatment (hospital, ward), diagnoses (primary, several secondary, permanent, and operation-related diagnoses), surgical procedures (operation length, urgency, ASA-classification; Table 2), ordered and transfused

blood components (estimated transfusion time, urgency, blood group), laboratory test values (lowest and highest hemoglobin, PLT values), as well as hospital admission and discharge variables (medical specialty, length of hospital stay, discharge status).

Table 2. *American Society of Anesthesiologists (ASA) Physical Status Classification.*

ASA-grade	
ASA I	Patient has normal health and normal operative and anesthetic risk.
ASA II	Patient has moderate systemic disease that does not limit activity.
ASA III	Patient has severe systemic disease limiting activity.
ASA IV	Patient has an incapacitating systemic disease that is a constant threat to life.
ASA V	Patient is not expected to survive with or without operation for 24 hours.

Year of hospital episode was defined by the starting date of the hospital visit. Thus, some of the previous years' visits continued into the next year.

The central database was saved to a remote server and accessed via the Internet by passwords.

4. Blood components

All blood components transfused to adults or children (RBC, FFP, PLT, cryosupernatant, white cells, whole blood, reconstituted blood) were gathered into the database. Blood components were expressed as units. Adult PLTs were described as a product (i.e. one PLT product containing four units of PLTs) in Study IV to be internationally clear. The main features of blood components (RBC, FFP, and PLT) used in our study are described below.

The main *RBC product* has been leukodepleted from the beginning of 2003, and one unit of RBCs has a volume of roughly 300 mL. It is manufactured from whole blood by centrifuging, removing the plasma, adding 100 mL of SAGM solution (sodium chloride-adenine-glucose-mannitol) and filtering. RBCs for small children are prepared by dividing an adult's product into three parts. One product, adult's or child's, is equal to 1 unit of RBC.

During the study period, the main *FFP product* was whole-blood–recovered leukodepleted fresh plasma frozen within 6 hours of donation and stored at <30°C. One product for adults was of approximately 270 mL containing 1 unit/mL of all normal plasma coagulation factors and physiologic anticoagulants. Plasma used for children was collected by apheresis. A single-donor apheresis plasma dose was divided into nine children's products (volume, 50 mL). One product, adult's or child's, is equal to 1 unit of FFP in the present study. The Octaplas® pharmaceutical product currently used was not included in any results of this study.

The main *PLT product* (98.5%) is prepared using the buffy-coat procedure and is preserved in PAS II-solution (sodium citrate, sodium acetate, sodium chloride, water). All PLTs are leukodepleted. One product of PLTs contains for practical purposes PLTs from four donors. One therapeutic PLT component thus contains 4 units. The volume of the PLT product is about 320 mL. The children's PLT product also contains 4 units of PLTs, but in a volume of 200 mL. Children's products were included in the results of this dissertation–although omitted from Study IV for consistency.

When *costs of blood components* were calculated, the price of each product was used separately (Table 3). Prices in different years were used, with no additional expenses (HLA typing, HPA typing, phenotyping, or emergency duty prices) taken into account. The cost of one RBC unit increased in 2003 when the RBC product most used became leukodepleted.

Table 3. *Costs of the most frequently used adult blood components in Finland.*

Year	Red blood cell (1 unit product; €)	Fresh frozen plasma (1 unit product; €)	Platelets (4 unit product; €)
2002	51.00	68.02	278.09
2003	90.10 (leukodepleted)	72.30	295.30
2004	92.60 (leukodepleted)	72.30	303.60
2005	95.10 (leukodepleted)	72.30	308.40
2012	120.40 (leukodepleted)	86.44 (Octaplas ®)	385.90

5. Quality assurance

Hospitals assisted in a systematic audit of data variables. For each hospital the audit was performed each year. Rough, unprocessed electronic data were first audited to insure a correct collection process and the collection of all desired variables. Then the pre-processed data to agree assembling and later the combined data were checked separately. The audit included such tasks as unifying code sets and comparing collected data to FRC BS sales figures and to figures reported by individual hospital districts (asked independently from each) and official national statistics (FHDR). Furthermore, distributions of processed variables were thoroughly studied, with data comparison between study years. The final audit included random sampling of the data for deviations. All deviations discovered during the auditing process were scrutinized further.

6. Study characteristics

Five studies were performed, based on transfusion data (Table 4).

Table 4. Study characteristics.

Study	Time period	Study subjects	Number of patients	Characteristics and variables
I	Two years (2002 and 2003)	Transfused patients	59,535	Age, gender, main diagnosis, main operation, red blood cell use during primary knee operation for primary arthrosis, transurethral resection of prostate and hysterectomy, costs of transfusion therapy
II	Two years (2002 and 2003)	Patients transfused with fresh frozen plasma	11,59	Age, gender, main diagnosis, main operation, laboratory test measurements
III	Two years (2002 and 2003)	Parturients admitted for vaginal delivery *and* having the lowest measured hemoglobin level, 70-100 g/L, *and* transfused with 0-2 units of red blood cells	1,954 (transfused 259 and not-transfused 1,695)	Age, type of vaginal delivery, proportion of red blood cell transfused patients, length of hospital stay
IV	Two years (2004 and 2005)	Platelet-transfused patients, particularly surgical platelet recipients	6,321 (3,399 of these with surgery)	Age, gender, main diagnosis, main operation, coronary artery bypass patients receiving platelets
V	Two years (2002 and 2003)	Transfused patients having surgery	33,196	ASA-grade, type of surgery

The study design was observational and data collection was retrospective.
Number of participating hospitals was 9 of 21.
Time period for each study, 2002 and 2003, expect for Study IV: 2004 and 2005.

7. Statistical analyses

All patients meeting the requirements were included. Patient populations were limited by diagnosis and surgical procedure codes.

The Ecomed Analyzer reporting program (version 6, Datawell Oy, Espoo, Finland), SPSS (version 12.0.1, SPSS Inc., Chicago, IL, USA) and R (Version 2.5.1 and Version 2.7.1, R Foundation for Statistical Computing, Vienna, Austria) served for analysis of the data.

For statistical analysis, ANOVA was used to calculate differences in blood component usage and costs (I) and to detect differences in duration of hospital stay (III). The Mann-Whitney U-test allowed analysis of differences in the last-measured Hb values (III) as well as differences in transfusion dose of PLTs between genders (IV). The T-test allowed a search for differences in transfusion age between genders (IV). Odds ratios were calculated to study association of PLT transfusion frequency and gender (IV). A logistic regression model was

constructed to study the probability of receiving RBCs during arthroplasty, and a scoring system was constructed from the odds ratios for each predictor variable (V). To check the validity of the model, receiver operating curves were constructed (V).

The results were expressed as mean ±standard deviation or median and range. A probability less than 0.05 was considered significant.

RESULTS

1. Validation of data (I)

In 2002 and 2003, 97% of the most commonly transfused blood components (adult RBC, FFP, PLT) sold by the FRC BS to the participating hospitals were found by comparison between hospital data and FRC BS sales information. RBC-use figures reported by participating hospitals produced a match in 94% of cases in a comparison with our established data system. Most hospitals acquired their data from the blood bank or invoicing systems. The number of primary knee replacement operations reported by the Finnish Hospital Discharge Register and our data matched by at least 98% in hospitals with more than 200 hip or knee operations per year. A random check, matching written data on primary hip replacement operations from one of the participating hospitals (Surgical Hospital in Helsinki) with collected computerized data, found a match in 99% of cases. ASA grade was recorded for 86% of procedures during 2002 and 2003 and for 90% during 2004 and 2005. The integrity of our data appears to be sufficient for comparative purposes and epidemiological research.

2. Finnish transfusion practices

2.1. Finnish blood component recipients (I, II, III, IV, V)

Data covered 117,248 hospital visits with transfusion (Table 5). All patients irrespective of age were included in the results of this dissertation (unlike in Study IV) for simplicity. Comparison with FRC BS sales figures revealed that our data included 54% of RBC sold during the study period, 71% of FFP units sold and 70% of PLT products sold (unpublished data from study I).

Table 5. *Study patients with transfusions 2002-2005. One individual patient can belong to several groups. (Some of these data are unpublished from Studies I and IV).*

Study year	2002	2003	2004	2005
RBC				
RBC-transfused patients	30 203	29 611		
Hospital visits for RBC transfused patients	40 798	40 593		
Transfused RBC units	142 260	138 960		
RBC-transfused surgery patients	19 010	18 025		
Hospital visits with RBC transfusion and surgical operation	20 267	19 210		
Transfused RBC units perioperatively	84 126	78 014		
FFP				
FFP-transfused patients	5 733	6 036		
Hospital visits for FFP transfused patients	6 204	6 527		
Transfused FFP units	28 940	31 300		
FFP-transfused surgery patients	3 814	3 957		
Hospital visits with FFP transfusion and surgical operation	3 924	4 077		
Transfused FFP units perioperatively	19 926	20 371		
PLT				
PLT-transfused patients	3 395	3 255	3 527	3 660
Hospital visits for PLT transfused patients	5 532	5 286	5 980	6 328
Transfused PLT units	95 784	89 146	91 360	98 652
PLT-transfused surgery patients	1 871	1 755	1 880	1 936
Hospital visits with PLT transfusion and surgical operation	1 930	1 811	1 932	2 024
Transfused PLT units perioperatively	32 947	28 390	29 264	30 832

RBC=red blood cell, FFP= fresh frozen plasma, PLT=platelet

Age of transfused patients

Most Finnish blood component-transfused patients were elderly (52% over 64), mean age 60 (SD 23) and median 65 (range 0-102); 6% of those transfused were under 16 and received 10% of the blood components.

FFP recipients were younger than all transfused patients; their mean age was 53 years (SD 27), median 62 (range 0-102). The percentage of FFP-transfused patients under age 16 was 16%.

Surgical PLT-transfused patients were also younger than blood recipients overall, at a mean age of 54 (SD 24.4) and median 60 (range 0-97). PLT-transfused men undergoing surgery were older than women (men 55, SD 23.0; women 52, SD 25.9; $p<0.001$). Only 8% of surgical PLT recipients were aged under 16. In short, blood recipients are most often elderly, but FFP and PLT recipients are younger than those blood-(or RBC-) transfused on average.

Transfused patients and gender

Blood component (RBC, FFP, PLT) -transfused patients were more likely to be women (56%). Males, however, received most of the blood components (54%). FFP recipients, in contrast, were more often men (58%), and men received also the majority of FFP units (60%). PLT-transfused surgical patients were also more frequently men (61%). This finding was statistically significant ($p<0.001$). Operated men also received most of the PLT components (60%), but between

genders, dosage of transfused PLTs was equal (mean dose of PLTs for men 15.02, for women 15.5; p=0.58).

Diagnosis of transfused patients

Half of all blood components (RBC, FFP, PLT) were transfused to patients with a hematological malignancy (20% of units), cardiovascular disease (16%), or trauma (13%). The greatest amounts of blood components were transfused to patients with myeloid leukemia (8% of units) and coronary heart disease (6%).

Patients with cardiovascular (26% of units) or gastrointestinal (17%) problems or trauma patients (16%) received the largest numbers of FFP units. The most common main diagnoses found among hospital visits involving FFP were: 1. coronary artery disease (4% of transfused FFP units), 2. atherosclerosis of arteries of extremities (3%), and 3. alcoholic cirrhosis of the liver (2%). The highest mean number of FFP units (5 units per hospital visit) was transfused to gastrointestinal patients, and 26% of FFP-transfused patients had cardiovascular disease as their main diagnosis.

Overall, the largest amounts of PLTs went to patients with malignant diseases of the blood as the main reason for their hospital stay (46% of PLTs). About 1% of surgical patients received PLTs, and perioperatively PLTs were mainly transfused to patients with cardiovascular problems (30% of transfused units to surgical patients), trauma (18% of units), and patients with digestive-system diseases (12% of units). The greatest number of PLTs per hospital visit involving a surgical procedure went to hematological cancer patients (mean 46 units per hospital visit).

Transfused patients and type of surgery

Surgical patients most often received blood components (RBC, FFP, PLT) in connection with operations involving the musculoskeletal system (27% of units transfused perioperatively; 34% of transfused surgical patients), gastrointestinal system (20%), or heart and major thoracic vessels (18%). The highest amounts of blood components were transfused to CABG patients (7% of perioperatively transfused units) or surgically treated hip-fracture patients (6%). The largest number of blood components per operative hospital visit was transfused to patients with infrarenal aortic aneurysm (27 units per hospital visit).

The majority of FFP were transfused perioperatively (67% of transfused units). The highest amounts of FFP were transfused during gastrointestinal surgery (25% of transfused FFP units), heart and major thoracic vessel surgery (23%) and musculoskeletal surgery (16%). Gastrointestinal patients received the largest number of FFP units per one hospital visit (6 units). Of FFP-transfused surgical patients, 25% underwent heart surgery.

Perioperatively transfused PLTs went to patients operated on for digestive system disease (25% of perioperatively transfused units), heart disease (25% of units), and musculoskeletal problems (14% of units). Most of these PLT

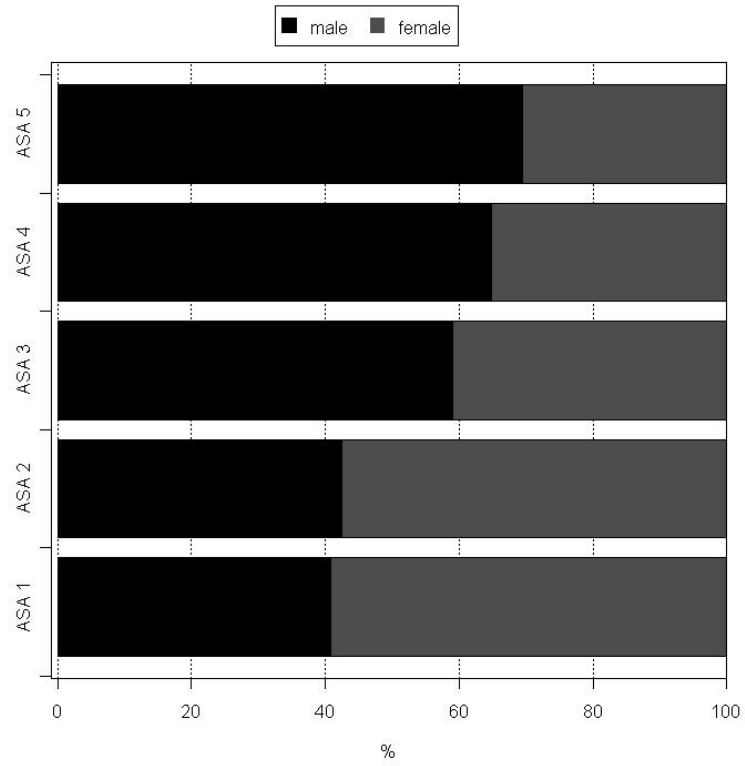
recipients operated on had coronary surgery (15%) or aortic valve replacement (5%).

Transfusion of PLTs and ASA grade

PLT-transfused ASA grade 1,2, or 3 patients were most often orthopedic or trauma patients (37% of hospital visits with transfusion), ASA-4 patients usually had heart surgery (7% visits with transfusion) and ASA-5 patients most often underwent gastrointestinal surgery (0.6% if visits with transfusion). ASA grade-3 patients received most of the blood components (36%).

PLT-treated operated men had a worse preoperative status than did women, judged by ASA grade (Figure 9). These men stayed longer in the hospital than did women (men 11 days, range 1-356; women 9, range 1-288) and had higher in-hospital mortality (men 13%; women 11%).

Figure 9. *Rate of PLT-transfused surgery patients by gender and ASA-grade.*



2.2. Blood usage (I, II)

Blood component usage differed between 2002 and 2003. Fewer blood components were transfused in 2003, and the number of transfused patients and hospital visits with transfusion dropped between those years (Table 6). Moreover, the average number of transfused blood components during hospital visits involving transfusion decreased. Reductions were concentrated among surgical patients. Perioperatively, fewer RBCs were transfused but an increase occurred in FFP use (Table 6).

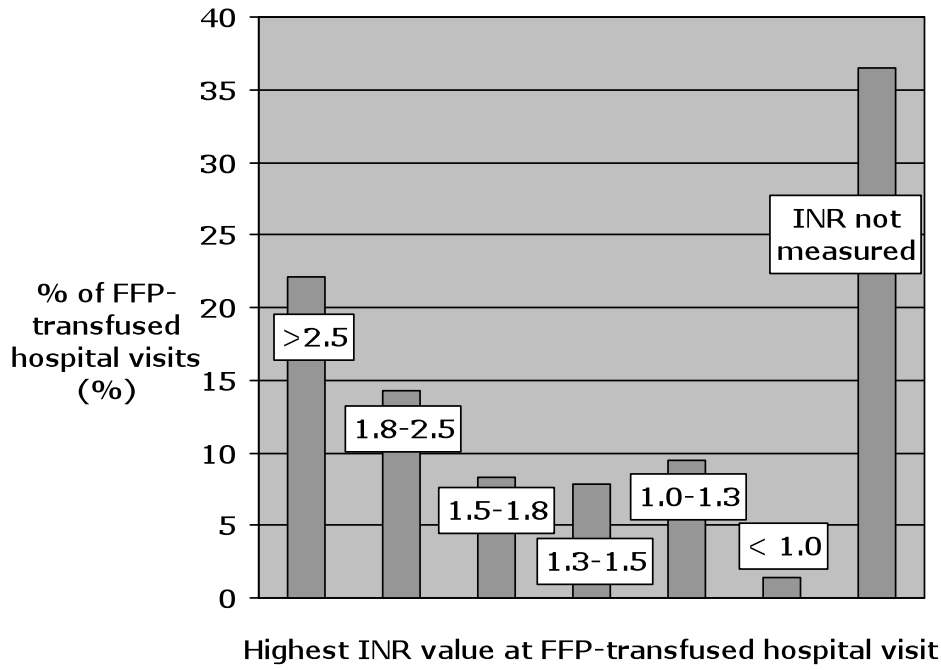
Table 6. *Blood use in Finland years 2002 and 2003*.

Year	Transfused patients (n)	Hospital visits with transfusion (n)	Transfused blood components (units)	Transfused blood components per hospital visit with transfusion (units/n)	Transfused surgical patients (n)	Hospital visits with transfusion and operation (n)	Perioperatively transfused blood components (units)	Number of transfused units per 1000 hospital visits with operation	
								FFP	RBC
2002	31 670	43 825	268 410	6.12	23 032	23 978	137 530	98	414
2003	31 307	43 753	260 694	5.96	22 159	23 057	127 286	100	385
Change from 2002 to 2003	-363	-72	-7 716	-0.16	-873	-921	-10 244	2	-29

2.3. Transfusion trigger practices (II, IV)

Coagulation (PT, INR, or APTT) associated with FFP transfusion was measured in only 66% of hospital visits (Figure 10), although coagulation parameters were checked somewhat more often during hospital visits including surgery (68%). The median for highest INR measurement rate during a hospital visit with FFP transfusion was 2 (range 0.8-11; mean 2.5). Furthermore, in 19% of hospital visits with FFP transfusion the highest measured INR was below 1.5.

Figure 10. *Rate of fresh frozen plasma (FFP) recipients by INR testing in 2002 and 2003.*



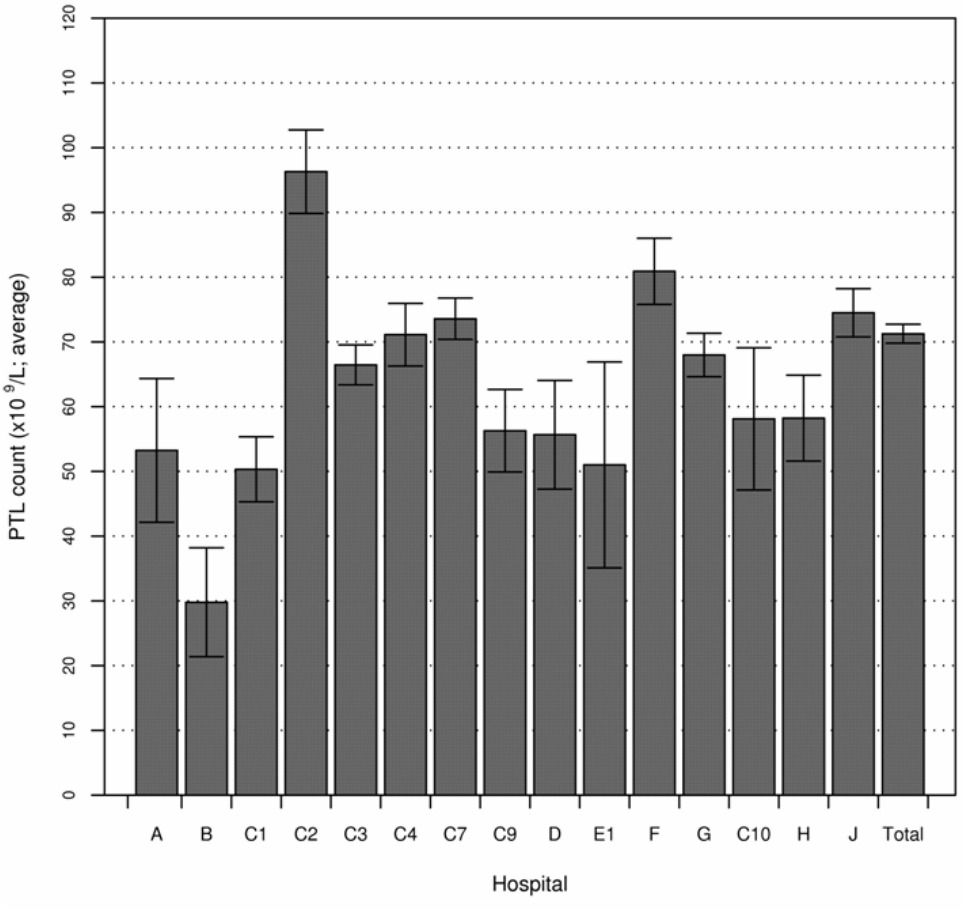
PLT count was measured at least once during almost every hospital visit with PLT transfusion and surgical procedure (99.5%) (unpublished data from Study IV). The mean of lowest PLT count in operated patients was $73x10^9$/L (SD

53X10^9/L). The difference between admission PLT count and lowest measured PLT count during the hospital visit suggests a higher percentage of transfusions for therapeutic than for prophylactic indications (Table 7). Transfusion-threshold PLT count varied between specialties and hospitals (Figure 11, Table 6). The difference between hospitals was statistically significant (p<0.001).

Table7. *Lowest measured PLT counts during hospital visits and PLT transfusion by medical specialty in patients undergoing surgery (2004 and 2005, unpublished data from Study IV).*

Speciality	Hospital visits (n)	Admission PLT count (x10^9/L; average)	Lowest PLT count (x10^9/L; average)	Discharge PLT count (x10^9/L; average)
Heart and thoracic surgery	1019	164	89	254
Neurosurgery	134	122	84	263
Urology	22	119	71	186
Others:not cathegorized	2085	155	67	268
Vascular surgery	108	148	67	234
Obstetrics and gynecology	133	137	66	279
Orthopedics	205	109	64	220
Gastroenterology	207	142	58	255
Plastic surgery	43	248	51	399
All specialities	**3956**	**153**	**73**	**261**

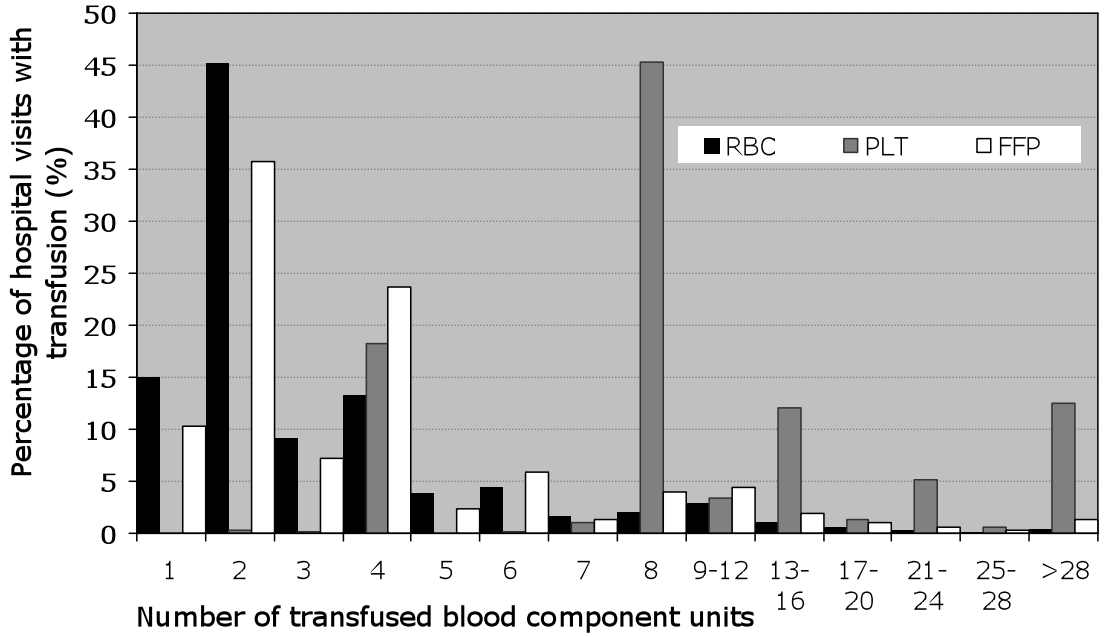
Figure 11. *Mean and SD of lowest measured PLT count during hospital visits of PLT-transfused surgical patients (2004 and 2005, unpublished data from Study IV).*



2.4. Dosage of blood components (I, II)

RBCs and FFP were transfused in paired and PLTs in 8-unit doses (Figure 12). Two units of RBC were given to 45% of RBC recipients, 36% of FFP recipients received a two-unit dose of FFP, and 45% of PLT-transfused patients receive 8 units of PLTs. The practice of two-product dosing is evident repeatedly in several subgroups of adult surgical patients (unpublished information).

Figure 12. *Rate of hospital visits with red blood cell (RBC), platelet (PLT), and fresh frozen plasma (FFP) transfusion by number of transfused blood units. Years 2002 and 2003.*



2.5. Costs of blood components (I)

Hematological malignancy and cardiovascular-disease patients generated the highest costs for blood components (19-26% of blood costs, 15-16%, respectively) (I). For surgical patients, most blood-component costs came from orthopedic patients (26-28% of costs involving surgery).

3. Comparison of transfusion practices among Finnish hospitals (I, IV)

We found variation in blood-component usage among hospitals. Percentage of RBC-transfused knee-replacement patients ranged between participants from 13% to 57% (Figure 13), and the average number of transfused RBC units

varied (mean 0.8 (SD 1-3; median 0, range 0-16). Variation in RBC-component use was confirmed in transurethral resection of the prostate (TURP) and hysterectomy (Table 8). Costs of RBCs per 100 operations showed multiple differences between institutions (I). PLT use in CABG patients also showed variability (IV).

Figure 13. *Mean of transfused red blood cell (RBC) units and percentage of transfused patients in unilateral knee replacement surgery for arthrosis in Finnish hospitals. Years 2002 and 2003. Hospital districts C and E include several separate hospitals.*

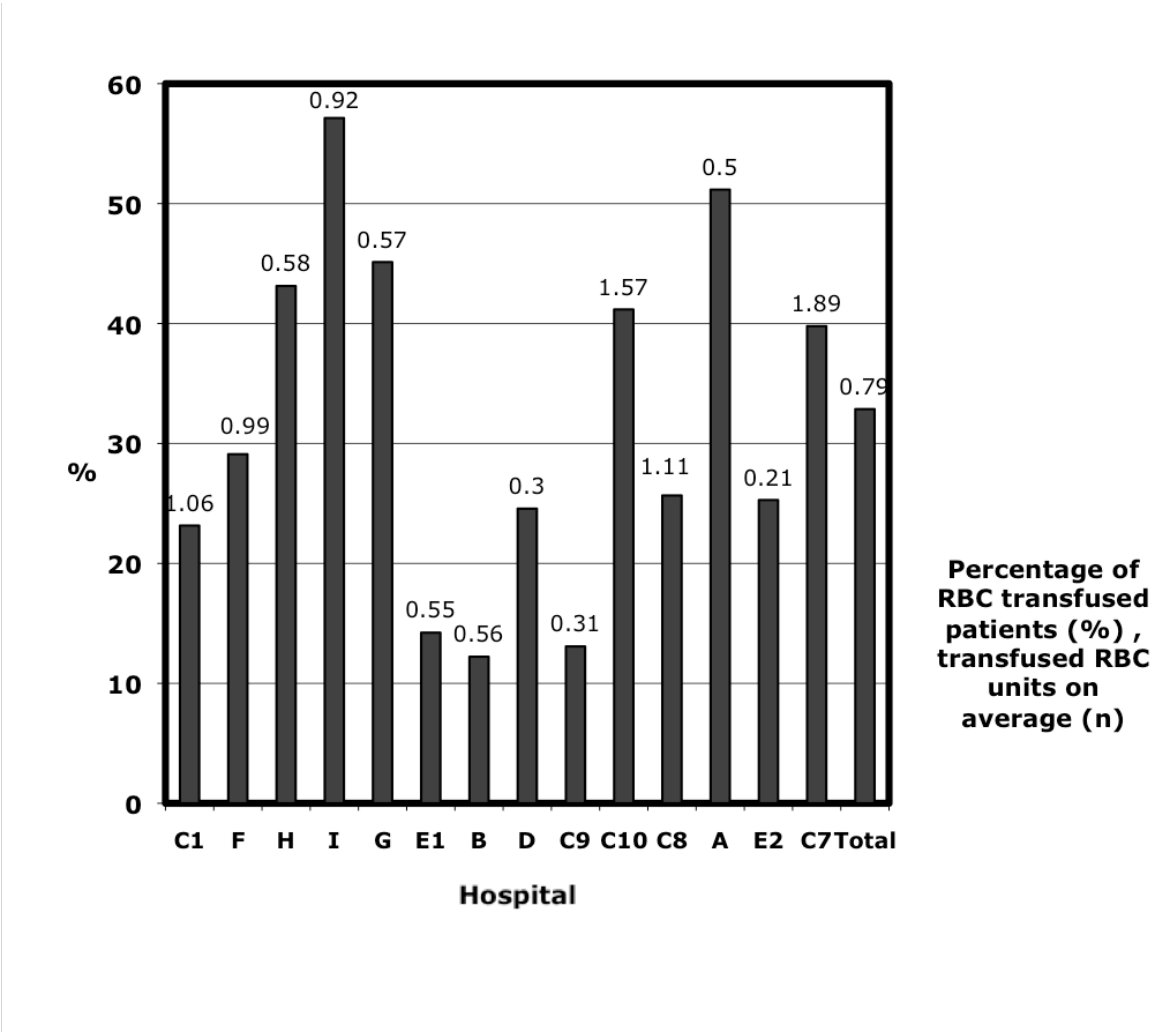


Table 8. *Red blood cell (RBC)-transfused patients undergoing transurethral resection of the prostate (TURP) and hysterectomy. Years 2002 and 2003. Hospital districts C and E include several separate hospitals.*

Hospital	Hospital visits with TURP	Percentage of operations with RBC transfusion (%)
C3	551	5.8
F	364	15.1
G	361	3.3
C9	228	11.8
I	207	5.8
D	200	9.0
C8	196	10.7
H	195	20.0
E1	187	10.2
C10	134	9.0
E2	125	11.2
B	123	18.7
A	39	2.6
Total	**2910**	**9.8**

Hospital	Hospital visits with Hysterectomy	Percentage of operations with RBC transfusion (%)
C4	1 082	8.2
I	477	6.5
C9	420	6.0
H	337	10.4
G	318	4.7
D	267	4.9
C8	233	11.6
F	164	14.0
E2	160	3.8
A	135	8.2
C10	135	8.9
E1	123	5.7
B	116	18.1
Total	**3 967**	**7.9**

4. Impact of red blood cell transfusion in a selected group of parturients (III)

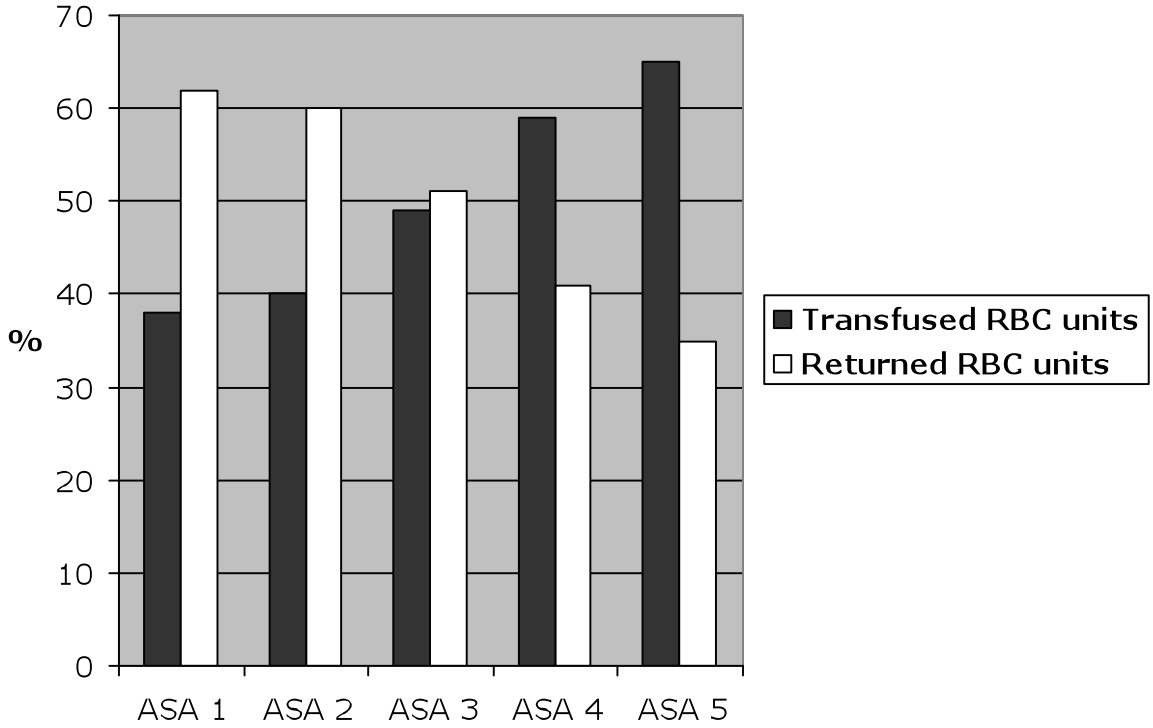
Study III evaluated RBC transfusion practice in a selected group of parturients. Patients admitted for vaginal delivery and having the lowest measured Hb value between 70 and 100 g/l and receiving 0 to 2 units of RBCs were compared in different Hb groups: 70 to 79 g/l, 80 to 89 g/l and 90 to 100 g/l. Only uncomplicated deliveries were included, and patients with surgical procedures or with recorded diagnoses affecting tolerance of anemia (for example cardiac disease) or increasing risk for bleeding (for example eclampsia) were excluded. The percentage of transfused parturients in this group was 13% (70-79 g/l, 70%; 80-89 g/l, 32%; 90-100 g/l, 1%). Mean duration of hospitalization did not differ statistically significantly between studied groups (70-79 g/l, for 5.4 days; 80-89 g/l, 5.2 days; 90-100 g/l, 5.1 days; p=0.33) or between transfused and non-transfused parturients within groups 70 to 79 g/l and 90 to 100 g/l (70-79 g/l, for transfused 5.4 days and non-transfused 5.2 days, p=0.50; 80-89 g/l, 5.1 days and 5.5 days, p=0.07; 90-100 g/l, 5.1 days and 5.4 days, p=0.54). Hospitalization of these anemic patients (Hb from 70 to 100 g/l) was distinctly longer than the mean stay of Finnish parturients (mean 5.2 versus 3.5 days).

5. Correlation between American Society of Anesthesiologist's (ASA) Physical Status Classification and transfusions (IV, V)

ASA grade correlated positively both with the number of transfused blood components and the percentage of transfused surgical patients, with more severely ill patients receiving more and also more frequent transfusions (V). Correlations were similar with all blood components when studied separately (RBCs, FFP, and PLTs). Especially those patients belonging to ASA grade groups 3 to 5 received more and also frequent blood components. Subgroup analysis of elective primary hip arthroplasty patients revealed a similar correlation with RBC transfusion and ASA grade (V).

In the general surgical patient population, RBC units ordered before surgery went more often to patients belonging to a higher ASA grade (unpublished data, Fig. 14). On average, 49% of all RBC units ordered were transfused at that time in Finland (Fig.14).

Figure 14. *Red blood cell (RBC) units ordered for surgery; percentage of administered and returned RBC units by ASA physical status classification (unpublished data from study V).*



There arose, however, a difference in correlation between genders in PLT-transfused patients. Male patients of a higher ASA grade group received PLTs more often than did women (the percentage of PLT-transfused men: ASA 1, 40%; ASA 2, 44%; ASA 3, 60%; ASA 4, 66%; ASA 5, 71%; women: ASA 1, 60%; ASA 2, 56%; ASA 3, 40%; ASA 4, 34%; ASA 5, 29%). Women, compared to men, thus received PLT transfusion more often at lower ASA grades.

An analysis predicting RBC transfusion in 3,271 primary total hip- replacement patients was performed, with a logistic regression model for RBC transfusion constructed and validated. The final prediction model included variables: ASA (I-II, III-IV), age (under 60 years, 61-70, 71-90, over 80), gender and preoperative hemoglobin value (under 90 g/l, 91 to 110 g/l, 111-130 g/l, 131-150 g/l and over 150 g/l). The area under the receiver operating curve for the resulting model in the training and validation data sets was 0.7 and 0.69, respectively. RBC transfusions were positively correlated with ASA grades III and IV, with age, female gender, and preoperative anemia. The percentage of RBC-transfused hip-replacement patients was high (65%). A clinical prediction rule for RBC transfusion was developed from the odds ratios generated by this model. Our scoring system identified patients with either high (predicted transfusion risk over 65%) or lower risk (predicted risk under 40%) for RBC transfusion.

DISCUSSION

1. Key results and strengths of the study

The data-gathering system established for this study was the first published national, annually accumulating database combining easily accessible information from several computerized registers to study blood transfusion recipients (I). Existence of a permanent, lifelong personal identification number used only in the Nordic countries enabled the combination of information collected from various sources. This system allowed us to investigate Finnish transfusion recipients and practices and to gather an information bank for our local healthcare professionals for benchmarking. This transfusion material included over 100,000 hospital visits with blood transfusion.

Our study register concentrated on more detailed information on the transfusion procedure and on transfusion recipients themselves. We also gathered blood-donation and detailed blood-component information, but did not use this information in our studies. These data were gathered only for quality assurance. In the same time period, published nationwide Scandinavian studies using a similar data-gathering process approached the subject of transfusions differently (Edgren et al., 2006; Kamper-Jørgensen et al., 2009). They sought to monitor the long-term outcome of transfusion recipients and included in their own transfusion register data values affecting mortality (death and birth variables, blood donation and component variables, cancer variables). The Danish Transfusion Database, which has been nationwide since 2006, includes similar transfusion-related information as the Finnish database presented to assess transfusion practices (Dansk Transfusionsdatabase, home page on the Internet). Blood transfusion-recipients' characteristics were similar to those of earlier international studies.

Our study on FFP use practices (II) was the first published national study including all FFP recipients (surgical and medical patients and also children) reporting also each FFP recipient's diagnosis and surgical procedures. Furthermore, our study reported figures of FFP use during surgery, giving baseline numbers for international comparison.

Unnecessary blood transfusions do occur also in Finland. Transfusion of 1 to 2 units of RBCs to moderately anemic parturients did not shorten the length of their hospital stay, suggesting possible over-usage of RBC in certain situations (III).

Most of the descriptive information on PLT use comes from hematological patients. Our national study reported perioperative use of PLT adding knowledge of characteristics of these blood recipients (IV).

Our comprehensive study population allowed us to study the association between blood transfusions and the more subjectively assessed variable ASA grade (V). Increased preoperative morbidity increased the possibility of receiving blood transfusion.

2. Generalizability and limitations of the study

The participating hospitals, situated in the most populated regions of Finland, constituted almost two-thirds of Finnish annual in-hospital visits (63% in the years 2002 and 2003; 64% in 2004 and 2005). Our data did not include all Finnish hospitals. No hospital districts without the technical ability to send computerized transfusion data were included. Furthermore, our study covered no Finnish primary heath care centers, nursing facilities, or private-sector hospitals. Neither did we include less frequent blood-component users, for example home-performed transfusions. Blood use at these less acute institutions is, however, uncommon and limited mainly to transfusion of RBCs. Our data included over 50% RBC units sold and roughly 70% of FFP and PLT products sold during the data period. Our study hospitals included 5 out of 5 of the Finnish university hospitals and a smaller portion of the other Finnish hospital districts.

From the methodological perspective, an obvious limitation to this study is that it is a register-based research. The focus of the registers differs from that of our study aims, limiting the data. Multiple sources of input error exist. For example, data are recorded in the information systems by numerous professionals with varying dedication and experience to fill in the required data. There may be a few cases not recorded or accidentally cases recorded multiple times. Mechanical, logical, and copying errors add to data inaccuracy. Subjectivity in recording ASA grade deserves to be mentioned separately as a variable limitation. Furthermore, these registers do not include all information necessary for transfusion research. For example, patient's weight and height or values of point-of-care laboratory measurements are absent.

Auditing is a prerequisite for register-based research. Technical data collection from different registers may fail, and pre-processing may produce technical errors. Hospitals have their own modifications or additions to the otherwise uniform software, which make the defining of, for instance, code sets laborious. For this research, over 2,000 code mappings were made manually to create uniform code sets (unpublished information). However, once this task of ensuring uniformity is completed successfully, analysis of data in the following

years requires much less effort. Validation is, nevertheless, needed on every occasion that new information is collected and especially when any changes are made to the software. The quality of the data gathered is assumed to improve at every collection. The accuracy of the recorded diagnosis and surgical procedures can be audited by comparison of the gathered information between handwritten hospital data or data collected in other available sources. Only random samples for comparison were taken between handwritten data (Surgical Hospital in Helsinki) and one easily accessible source of computerized data (the Finnish Hospital Discharge Register). An audit was done concerning arthroplasty patients.

Because of the limitations in study material collection, single or small groups of treatment episodes cannot be compared or examined separately. It is essential that the amount of information studied is large enough. Only the most accurate data variables estimated by the validation process are appropriate for research.

Similar data gathering processes and validation results from Danish researchers indicate the rationality of our approach. Validation of electronic patient information gathered from six different computerized registries in Denmark found 98% integrity of all blood-component transfusions, and 95% of them did connect with a main diagnosis (Titledstad et al., 2002). Danish data-gathering and validation processes were similar to ours (Titlestad, personal communication). Both groups used permanent personal identification numbers provided by national authorities for connecting transfusion-related data from different information systems.

3. Blood component recipients

Age of transfused (RBC, FFP, PLT) patients

Other studies confirm the finding that elderly patients represent the majority of all transfusion recipients (Mathoulin-Pelissier et al.2000; Tynell et al., 2001, 2005; Kamper-Jørgensen et al., 2009; Appendix 2). The aged patients in our study received a larger proportion of transfused blood components than in the Zimmermann group study (1997), but that German study was conducted in one study hospital only. Results from other Nordic countries (Denmark and Sweden), on the other hand, resembled our findings (Kamper-Jørgensen et al., 2009). In the present study, children (6.2% of transfused patients) received about 10% of all transfused blood components, a finding agreeing with a finding in the U.K. (Stanworth et al., 2002). Related figures were lower in Denmark, Sweden, and Spain, but higher in the USA (Vamvakas and Goldsten, 2002; Kamper-Jørgensen et al., 2009; Bosch et al., 2011). Dissimilarities in the data sample and in cut-off ages might explain these differences.

Ages of FFP and PLT recipients

A Finnish finding of almost half of FFP units being transfused to patients over age 60 differs from the U.K. and Danish practice, where a larger proportion of FFP goes to this elderly patient group (Cobain et al., 2007; Appendix 2). The cut-off ages do not match those of studies from the USA, Australia, and the Netherlands, but their usage practices seem similar to ours (Vamvakas and Taswell, 1994; Cobain et al., Australias' data, 2007; Borkent-Raven et al., 2010; Appendix 2). In a Dutch study with age-grouping in children similar to that in our study, children received fewer of all transfused FFP units, but the patient population included only academic hospitals (Borkent-Raven et al., 2010). Children's cut-off age varied among other reported FFP-transfusion data, explaining the differences (0-9 and 10-19 years for Cobain et al. compared to 0-15 years in the present study) (Cobain et al., England's and Denmark's data, 2007). We found the Finnish FFP- and PLT-transfused patients to be younger than transfused patients in general, agreeing with other studies (Cook and Epps, 1991; Tynell et al., 2001; Greeno et al., 2007; Cobain et al., 2007; Wells et al., 2009; Borkent-Raven et al. 2010; Stanworth et al., 2011).

Transfused (RBC, FFP, PLT) patients and gender

That women are being transfused more often with blood components (altogether) than are men is in agreement with others' findings (Whyte, 1988; Mathoulin-Pelissier et al., 2000; Tynell et al., 2001, 2005; Titlestad et al., 2002; Kamper-Jørgensen et al., 2009; Madsen et al., 2010; Appendix 3). Because RBC recipients comprise most of our study patients (Table 4), this finding could at least in part be explained by female patients' having initially lower base-line Hb concentrations and red cell mass. When patients with the same Hb concentrations (g/l) are compared, patients with a lower blood volume, such as females, bleed less to drop to the same Hb count than does a patient with a higher blood volume. This may increase the susceptibility to transfusion of patients with smaller body sizes. However, one study in patients undergoing CABG surgery showed that female gender was still significantly associated with RBC transfusion even when the genders compared were within the same subgroups for age, weight, duration of surgery, and preoperative hematocrit (Shevde et al., 2000). Age standardization in one Danish study resulted in evidence of men's higher transfusion prevalence rates (one-year prevalence rate 6.8/1,000 for men and 6.3/1,000 for women) (Madsen et al., 2010). Differences in age distribution between genders are accounted for when comparing transfusion databases. There is evidence supporting a role for sex hormones in altering the hemostatic balance (Lawrence et al., 1995; Mendelsohn, Karas, 1999). For example, use of oral contraceptives is clearly associated with an increased risk for thrombotic events. However, due to the complexity of the mechanism involved in the coagulation system, a gender difference in one or more hemostatic components may not lead to an apparent difference in overall

hemostasis (Capodanno, Angiolillo, 2010). Differences in hemostatic balance between genders may not explain the gender-specific differences in the likelihood of transfusion.

FFP recipients and gender

That more men were transfused with FFP, and men received a larger proportion of FFP than did women agrees also with several other results (Cook and Epps, 1991; Zimmermann et al., 1997; Cobain et al., 2007; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011; Appendix 3). Men are over-represented in certain patient groups requiring FFP (for example CABG, gastrointestinal bleeding, and trauma) (unpublished information from Study II), and this finding may also result from their larger body size and also reflect dosing by weight.

PLT recipients and gender

Finnish male patients received more of the PLTs used perioperatively and received them more often than did female patients. Even though we studied only a particular subgroup of PLT recipients, other work confirms this finding (Cook and Epps, 1991; Zimmermann et al., 1997; Cobain et al., 2007; Wells et al., 2009; Borkent-Raven et al., 2010; Bosch et al., 2011; Appendix 3). This observation might in part be explained by the finding of male PLT recipients' having a worse preoperative status than did women, as well as their greater body size, and may thus reflect PLT dosing by weight.

Diagnosis of transfused patients

In Finland, cancer and cardiovascular disease patients received most of the blood components, in agreement with Swedish findings (Tynell et al., 2005).

Circulatory or digestive system diseases represented in our study the most FFP-transfused diagnostic groups, as in five other studies (Cook and Epps, 1991; Cobain et al., 2007, Denmark's data; Wells et al, 2009; Borkent-Raven et al., 2010; Bosch et al., 2011; Appendix 4). Our findings differed from French, German and Korean findings including in their analyses either a smaller sample of patients or fewer hospitals (Zimmermann et al., 1997; Mathoulin-Pelissier et al.2000; Lim et al., 2004). This dissimilarity probably therefore reflects a difference in patient material. As in Denmark and Spain, also in Finland the most common diagnosis of FFP-transfused patients is coronary artery disease (Titlestad et al., 2001; Bosch et al., 2011; Appendix 5).

Transfused patients and type of surgery

Our data included fewer patients with coronary artery surgery and blood-component (RBC, FFP, PLT) transfusion than did a Swedish study (7% versus 14%) (Tynell et al., 2005). The percentage of transfused femoral fracture

patients was almost double ours in the Swedish data (6% versus 11%)(Appendix 6).
Two-thirds of FFP units were transfused to patients having surgery, which matched the findings of Cook and Epps (1991), and two-thirds of FFP recipients were surgical patients.
About 10% of our patients undergoing CABG received PLTs. PLT use during CABG was similar to that of previous findings (Sirchia et al., 1994; Kytölä et al., 1998; Stover et al., 1998).

4. Blood component usage

This snapshot of Finnish blood transfusion use shows a trend towards a decrease in RBC use in contrast to FFP consumed. Annually PLT transfusion rates seem to vary more (I, Table 4). Variation in overall blood use between the years studied result from various causes, arbitrary or otherwise.

Adequate comparison of Finnish blood component usage with international usage requires accepted and uniformly defined attributes. At the moment, published statistics are inconsistent.

The FRC BSs´ annual sales figures confirm our finding of decreasing RBC use in Finland (Figure 1). In contrast to this, the trend in many countries has been toward an increase. The RBC transfusion trend in the USA in 2001 compared with 1999 shows a large increase, differing from our figures (Sullivan et al., 2007). This rising trend of RBC use in the USA seems to be continuing (National Blood Collection and Utilization Survey Report, 2009). A significant part of RBC use variation *per capita* can be explained by differing age distributions of populations, because RBC transfusion frequency increases with age (Ali et al., 2010).

5. Transfusion trigger practices

5.1. Transfusion of fresh frozen plasma

New guidelines recommend transfusing FFP guided by coagulation parameters for assessment of the need and the efficacy of FFP transfusion (O'Shaugnessy et al., 2004). Our study results indicate that these guidelines are not followed by clinicians (II). This Finnish finding agrees with those of a European study (Sirchia et al., 1994). In the Sanguis study, PT levels were measured in only 16% of FFP-transfused surgical patients. Our result showed wider acceptance of coagulation-test monitoring with FFP transfusion (about 66%). However, this Finnish finding differed from Australian findings from one tertiary hospital; in their clinical audit study, 92 to 97% of FFP recipients had coagulation parameters available or only requested (Hui et al., 2005). Better acceptance of

coagulation screen tests (93%) was also observable in the U.K. (Stanworth et al., 2011). The difference from the Finnish figures may involve dissimilarities between studied institutions and may also involve availability of the coagulation tests or different implementation of FFP transfusion guidelines.

Similar results to our Study II were reported by the ANZICS Group in an intensive-care patient group of 874 from Australia and New Zealand (Blood Observational Study Investigators of ANZICS Clinical Trials Group, 2010); 26% of FFP transfused did not agree with the national guideline cut-off value of INR 1.5. Adbel-Wahad et al. (2006) concluded in their study of FFP-transfused patients with a pretransfusion INR between 1.1 and 1.85 that in less than 1% of the patients did the INR level normalize, and only 15% showed a correction at least half-way to normal with FFP transfusion, regardless of the number of FFP units transfused. Cheng and Sadek (2007) and Stanworth et al. (2011) found similar results. These study findings do not justify FFP transfusion in nearly one-third of Finnish FFP-transfused patients with mild coagulopathy.

5.2. Transfusion of platelets

Our unpublished data show that nearly all Finnish surgical PLT recipients had PLT counts available. This agrees with the Australian figure (Hui et al., 2005). Our mean pretransfusion PLT count in surgical patients ($73x10^9$/L) agrees with present guidelines, which recommend PLT dosing at trigger values of 50 to $100x10^9$/L depending on type of surgery (Samama et al., 2006). Those in cardiac and thoracic surgery specialties seem, however, to apply PLT transfusion thresholds higher than recommended (Table 4).

The PLT count triggering PLT transfusion in surgical patients was higher in our study than in the study of Arnold et al. (2006) in ICU patients (therapeutic trigger $51x10^9$/L, prophylactic trigger $41x10^9$/L). They excluded trauma, orthopedic, and cardiac-surgery patients, which explains at least part of this dissimilarity. Cameron et al. (2007) studied 25 surgery patients of 464 receiving PLTs in a referral hospital in Canada. They found the mean pretransfusion PLT count to be $84.5x10^9$/l, slightly higher than in our patients. In Australia and New Zealand, a multicenter study of 874 ICU patients showed a mean transfusion PLT count of $67.0x10^9$/l (Blood Observational Study Investigators of ANZICS Clinical Trials Group, 2010). They concluded that 53% of PLTs were not transfused adherent according to national guidelines (Council NHAMR, 2001). This dissimilarity may involve differences in the type and number of patients stemming from the differing profiles of the participating hospitals.

PLT transfusion are required when a patient is severely thrombocytopenic or bleeding due to platelet dysfunction. Transfusion of platelets has been

associated with increased risk for in-hospital mortality in massively transfused patients according to Rose et al. (2009), who discussed whether platelet transfusion per se influences mortality during massive transfusion or only reflects the severity of patients' underlying condition. Our findings support the latter in male patients (IV). Unfortunately we did not study massively transfused patients separately to find the possible association between the 1:1 transfusion ratio of FFP:RBC and lower in-hospital mortality, as suggested by Rose et al. (2009). One retrospective study of leukemia patients over a 10-year period found that the higher the dose of transfused platelets, the lower the survival in leukemia (Blumberg et al., 2008). Those patients receiving higher doses of PLTs required more and other transfusions as well. This finding suggests that patients receiving more PLTs need more chemotherapy and longer treatments to bring their leukemia into remission, reflecting severity of the disease (Blumberg et al., 2008). PLT transfusion affecting mortality during cardiac surgery is a study topic (McGrath et al., 2008). A retrospective study from Cleveland included 32,298 patients undergoing CABG, isolated valve, or combined CABG valve surgery, all requiring cardiopulmonary bypass. After propensity matching analysis, PLT transfusion did not confer an independent increased risk for adverse events. PLT transfusion did not lead to increased morbidity, neither in heavily RBC-transfused cardiac surgery patients nor in patients receiving no RBC transfusions.

6. Dosage of blood components

6.1. Dosage of red blood cells

RBCs being transfused in paired units in Finland probably arises from a traditional rule of thumb: transfusion of one RBC unit is usually ineffective. Clinicians seem to have adopted this rule uniformly (I, Figure 5). The practice of dosing with two RBC units per transfusion occasion is in concordance with other findings (Titlestad et al., 2001; Shapiro et al., 2003; Gombotz et al., 2007). Observations by Surgenor et al. (1989 and 1991) differed from ours. Their patients with gastrointestinal diseases or knee' and hip-replacement received whole blood or RBCs according to a more linear trend. Only one-unit transfusions were uncommon.

The paired use of RBCs deserves further discussion. It has been argued that one-unit RBC transfusion is inadequate for correcting anemia and exposes patients to needless risks from transfusion (Micolonghi et al., 1966; Reece and Beckett, 1966). Later, use of single-unit transfusions by hospital transfusion committees was discouraged (Grindon et al., 1985). Newer randomized study information suggests a lower transfusion threshold than 20 years ago (Hebert et al., 1999). This has led to a change of this recommendation and has been

supported by a retrospective study (Hebert and Fergusson, 2004; Ma et al., 2005). Ma et al. retrospectively estimated the effect of one-unit RBC transfusion reaching the targeted Hb count over the range of Hb triggers from 70 to 90 g/l in patients transfused with one or two units of RBCs. They found that single-unit RBC transfusion raised Hb concentration sufficiently in most patients. For this reason, routine paired dosing of RBCs can be questioned.

6.2. Dosage with fresh frozen plasma

Here we found that FFP was also transfused in paired-unit doses (I, Figure 5). The observation as to paired FFP dosage is similar to that in a Danish study and a study on elective CABG patients in the USA (Titlestad et al., 2001; Covin et al., 2003). The explanation for this practice cannot be found easily and is not supported by transfusion guidelines. National guidelines recommend body weight-adjusted dosing (10-15 ml per kg). Following of this guideline would produce for an average-weight person (70 kg) a transfusion of three to four units of FFP (270 mL per one unit), not two. In clinical situations, most often two-unit FFP transfusions are related to reversal of the warfarin effect in patients unable to tolerate the full volume of the suggested dose. This clinically observed practice has been confirmed by a study from Australia (Hui et al., 2005). Chowdhury et al., (2004) showed in 22 critically ill patients (of who 10 had required no FFP) that currently guided FFP dosage (12.2ml/kg) raised coagulation factor levels above the targeted levels (30 IU/kg, 1 g/l for fibrinogen) in only one of five patients, but 33.5 ml/kg dosage achieved the target in all seven.

Dara et al., (2005) retrospectively studied 115 critically ill patients with INR≥1.5 and without active bleeding. They found that FFP transfusion corrected the INR value in only 36% of these patients. The median dosage of FFP was higher in patients whose INR was corrected than in patients in whom it was not (17 ml/kg vs. 10 ml/kg).

Stanworth et.al. (2011), studying FFP use in critical care, included in their research 29 adult general intensive critical care units and studied 1,923 admissions with 1,212 FFP units transfused. Their median dose was 10.8 ml/kg (ranging first to third quartile from 7.2 to 14.4 ml/kg). Only marginally higher volumes of FFP (typically just one additional FFP unit) were prescribed in association with bleeding and an elevated INR than for non-bleeding patients. Their data suggest that doses of FFP were inadequate, too small. Although the optimal dosage of FFP is uncertain, smaller doses do correlate with poorer treatment response.

6.3. Dosage of platelets

PLTs were transfused most often in 8-unit doses. National guidelines recommend adjusting the PLT dose to the patient's body size (1 unit per 10 kg), thus explaining this finding. This Finnish study result differed from Danish findings in which recipients were transfused in a more linear fashion (Titlestad et al., 2001). One comparison of three different prophylactic doses of PLTs for hematological thrombocytopenic patients based on body surface area had no effect on incidence of bleeding (Slichter et al., 2010). Similar results appeared in two smaller studies earlier (Tinmouth et al., 2004; Heddle et al., 2009). The Strategies for Transfusion of Platelets study was, however, halted because the study limits were reached. A 5% absolute difference in grade-4 bleeding (including debilitating bleeding, nonfatal central nervous system bleeding or fatal bleeding) between study groups was reached after enrollment of only 119 patients. This study differed from that of Slichter et al. (2010) by its using standard doses of PLTs not adjusted for body-surface area. The optimal dosage of PLTs for prophylaxis thus remain unclear.

7. Transfusion practices

In *orthopedic patients*, the percentage of RBC-transfused patients among all patients undergoing knee replacement, as well as the mean number of transfused RBC units has fallen since the 1990s in Finland (from 84% to 33%, from a mean of 2.6 to 0.8 RBC units) (I; Capraro, 1998). A study from Canada found an even lower RBC transfusion ratio in primary knee-replacement patients (16.5%) (Feagan et al., 2001). Our benchmarking data published on the Internet shows a similar trend in RBC use for primary hip-replacement patients (Standard reports, database on the Internet, 2006). The decrease in Finnish RBC requirements in orthopedic patients may have resulted from evolved surgical techniques, increase in use of blood conservation methods, and a lowered Hb trigger for RBC transfusion. The difference from international data might be explained by the same variables.

Our data included 2,910 *TURP patients* with an RBC transfusion rate of 10% (range 3-20%). Earlier data from Finland showed a transfusion percentage of 18% with the TURP procedure (range 7-31% between hospitals) (Capraro et al., 2000). Robertson et al. (1993) had reported a lower rate of RBC recipients (11%; mean 2.6 units, range 1-7). The same kind of decrease in percentage of transfusion recipients emerged in the Uchida et al. (1999) study; the transfusion rate in TURP patients in Japan decreased from 20% in 1971-1985 to 6% in 1985-1996.

The results of this thesis show that 8% of *patients undergoing hysterectomy* for uterine fibroids received RBCs, a transfusion rate almost twice as high as in

institution studies from the USA (3%) and Australia (5%) (Ng, 1997; Kohli et al., 2000). Differences in study sample sizes (3,967 versus 491 and 3,967 versus 236) and dissimilarity of the institutions may also explain part of this dissimilarity. Conversely, Dicker et al. (1982) found a transfusion rate almost twice as high as in Finland (13%).

The percentage of PLT recipients among *CABG patients* ranged between Finnish hospitals from 7 to 14% (mean 9%). This result was similar to previously reported data from Finland (9%, range 2-22%) and from the USA (10%, range 4.8-18.4%) (Kytölä et al., 1998; Covin et al., 2003). Reasons for this persistent high rate of PLT use went unstudied. It is conceivable that improvements in PLT salvage based on improvements in surgical techniques, for example increase in off-pump CABG, are not evident because over the same time-period, anti-platelet-agent use increased. Variability in the present study was less than in an earlier Finnish study by Kytölä et al. (1998), suggesting more consistent PLT transfusion practices within Finnish hospitals.

8. Parturients

The finding of RBC transfusions' not shortening the length of hospitalization in a selected group of parturients suggests the possibility of unnecessary RBC transfusions. Dickason and Dinsmoor (1992) studied 899 patients who delivered by caesarean section. They found 7% of them to receive RBC transfusions (mean 2.8±1.4 units). Transfused patients were hospitalized longer than the non-transfused (mean hospital stay 6.1±3.9 versus 5.0±1.5 days, p=0.032). The lowest Hb and the hospital-discharge value of Hb, as well as estimated blood loss, differed between RBC recipients and non-transfused patients (respectively, lowest Hb 76±14 g/l versus 100±14 g/l; discharge Hb 94±12 g/l versus 100±13 g/l; estimated blood loss 1468±706 ml versus 879±198 ml). These study results differed from ours: their discharge Hb value was lower in transfused patients, disparate from our present findings. Estimated blood loss was almost double in transfusion recipients, and the lowest Hb values differed between groups. The patient groups thus differed between these two reports. Furthermore, a metanalysis of randomized and restrictive versus liberal RBC transfusion groups found no difference in length of hospital stay for Hb triggers between 70 and 100 g/L, agreeing with our finding (Carless et al., 2010). However, anemia, per se, lengthened the hospital stay of parturients in the present thesis study. As mentioned by Asakura et al. (2007) mere following of the Hb-level, even in an otherwise healthy mother, does not suffice to prevent unnecessary transfusions. A retrospective study based on chart review on obstetric in-patients in the USA found 34% of RBC-transfused mothers without any written indication for transfusion, with the majority of these patients (80%) receiving only 1 to 2 units of RBCs (Butwick et al., 2009). Findings from USA supports our finding suggesting inappropriate RBC transfusions in this patient

population. Our nadir and discharge Hb values were higher than these from the USA, based on the difference in study populations, the US study including also complicated pregnancies and deliveries.

9. Prediction of blood need

The increasing blood need in the future calls for amendment of practices to avoid a blood shortage. One simple way of improving the blood use routine is to target blood orders to the patients needing them most. Correctly targeted blood orders reduce blood wastage, minimize blood storage and blood-storage times, reduce expenses, and enable more rapid use of blood products.

Scoring systems to predict the massive RBC need for trauma patients have been developed (Yücel et al., 2006; Nunez et al., 2009; Mitra et al., 2012). German and Australian studies used patient variables such as gender, hemoglobin value, and severity of disease to estimate the need for transfusion, similarly to our study (Yücel et al., 2006; Mitra et al., 2012). The US study did not include laboratory parameters or gender and used only severity of disease and clinical values such as blood pressure and heart rate for prediction (Nunez et al., 2009). These scores designed for trauma patients performed better than our score system for hip arthroplasty patients, but trauma studies chose more specific parameters for severity of disease (free abdominal fluid, type of fracture, Glasgow Coma score) than the rough ASA classification in our prediction model. Furthermore, the patient populations in these studies differed (massively bleeding trauma patients versus elective hip-surgery patients).

At the time of our study, the normal routine for hip arthroplasty surgery was an order of 4 units of RBCs pre-operatively. Our score could have been used in a clinical situation: patients with scores from 0 to 40 (predictive transfusion risk under 40%), order of 0 to 1 RBC units; scores from 40-80 (transfusion risk 40-80%), order of 2 to 3 units of RBCs; patients with scores over 80 (transfusion risk over 80%), order of 4 units. This approach should be tested in clinical use before implementation.

10. Influencing blood component use

The present study was observational, and patient care was not standardized or purposely influenced in any way. However, our data-gathering system enables this kind of pre- and post-intervention research, and the subject of influencing blood component use calls for discussion. Blood component use indications have changed over the years, with new study information and emphasis on more restrictive use. Transfusion medicine specialists have put much effort into education and into informing transfusing personnel of changing indications.

Amendment of practices is, however, laborious and slow, and many different approaches have been tried. Blood-use guidelines (local or national), educational efforts (material and sessions), reminders of appropriate blood use and auditing (retrospective and approving transfusion requests) have been tried and studied (Barnette et al., 1990; Hawkins et al., 1994; Lam et al., 1997; Toy et al., 1998; Pentti et al., 2003; Kakkar et al., 2004; Müller et al., 2004; Hui et al., 2005; Rana et al., 2006; Leal-Noval et al., 2011). Two systematic reviews failed to determine what type of intervention might be more effective than others in reducing inappropriate blood use practices but concluded that "Even simple interventions may be effective" (Wilson et al., 2002; Tinmouth et al., 2005). However, in a recent metanalysis, organizational interventions concerning FFP usage have shown a positive impact in reducing inappropriate FFP transfusions (Damiani et al., 2010). The need for prospective, randomized, matched-pair-designed studies was acknowledged. Altering blood-use habits requires from the personnel performing transfusions a desire to change (Tinmouth, 2007).

Our study results we discussed first in 2004 with a small group of Finnish transfusion professionals involved with data gathering. Later, we organized sessions reporting benchmarking data to transfusionists involved with orthopedics, heart surgery, obstetrics, and hematological patients. The influence of these gatherings on study findings is possible.

11. Clinical implications

The optimal practice of transfusion therapy depends on three factors: blood donors, clinical practice, and societal forces. Availability of suitable and willing donors has an effect on the availability of blood components; clinical practice influences the amount of needed blood, and societal forces (resources, legislation) affect both. The optimum of transfusion practice is also location related and changes over time. Continuous monitoring of varying blood component use provides us with information on transfusion practices and produces data available for comparison. Knowledge of change and variation may serve to improve transfusion therapy. Our research database and annual data collection process provide Finnish healthcare professionals a foundation for benchmarking. More annual data on Finnish transfusion practices are vital to discover and to explain changing trends in blood use and to identify the best areas for change. Any new practice that is simple to use, and safe for patients, and that leaves the decision to transfuse or not up to transfusion providers may help us improve our transfusion practices. Evidence-based guidelines and patient management program including optimizing erythopoesis, reducing bleeding, and tolerating anemia may improve the availability of blood products to the aging population (Leahy, Mukhtar, 2012).

RBCs are transfused in two-unit pairs, but this practice of transfusing two units at the same time is outdated. Newly recommended lower RBC transfusion thresholds can be accomplished by transfusing just one RBC unit at a time. The decision to transfuse RBCs can be made individually, and if patients tolerate anemia, clinicians can, too.

FFP is transfused also in two-unit pairs. Transfusing FFP should be guided by coagulation parameters to assess the efficacy of treatment. An insufficient number of coagulation measurements are taken at the moment suggesting use of FFP as volume replacement.

PLT transfusions are common also perioperatively; not only hematological patients receive PLTs. Gastrosurgical patients and heart surgery patients most often receive PLTs perioperatively, making them an easy choice for improvement efforts for PLT use. Transfusion of PLTs is guided mostly by measuring PLT count in surgical patients.

Unnecessary blood ordering prolongs the storage time of blood components and strains the decreasing future blood supply. All efforts to minimize unnecessary blood orders and possible wastage of blood components improve patient care.

12. Future perspectives

Although improvements in care and implementation of blood salvage protocols reduce the need for transfusions, this trend is counteracted by the change in demography of the patient populations. Aging of the Finnish population leads to increased future need for blood components, especially for RBCs. To provide for the increasing requirement, requires more dedicated blood donors. Recruiting new donors from the decreasing eligible population will be the upcoming challenge for blood-collection organizations. Demand for safer blood products further raises the future costs of blood transfusion therapy. Artificial oxygen carriers are under constant research but most likely will not replace RBCs in the near future.

A PLT transfusion increase is expected. A growing number of intensive treatment regimens for hematological and other malignancies and increasing use of new anti-platelet drugs will raise the number of PLT recipients, as will the aging population. FFP use may, on the other, hand decrease or at least even out. Coagulation factor-concentrate therapy seems to be increasing as products improve and prices become comparable. Easy accessibility and low infection risk makes these coagulation concentrates attractive. Furthermore, the use of point-of-care coagulation tests is increasing, facilitating the use of these concentrates. Scientific evidence on their efficacy and safety is essential.

A need is widely acknowledged for randomized, controlled studies to optimize transfusion therapy practice. Clinical studies on effectiveness, appropriate dosage, and transfusion-trigger values for FFP and PLT use are crucial.

Additional Finnish transfusion data has been gathered and reported on the FRC BS Internet pages. Improvement of this kind of transfusion database includes adding more parameters, such as patient's weight and height, point-of-care measurement values, use of anticoagulation, indication for transfusion, and blood loss, when such data are entered into hospital computerized registers. Combining hospitals' transfusion-recipient information with FRC BS blood unit information, which is technically possible at the moment, would help in evaluating the relation between the age of blood units and morbidity or incalculating the wastage of blood products. Hopefully, an enthusiastic group of physicians with special interest in transfusion therapy will form, combine their research data, and share transfusion-related information.

CONCLUSIONS

Data on hospital electronic systems can be combined and used to study transfused patients and transfusion practices.

1. The variability still evident in Finnish transfusion practices between hospitals is suggestive of inappropriate use of blood components. The practice of transfusing RBCs in two-pair units is questionable. Newly published data recommend lower hemoglobin thresholds for RBC transfusion, which can be accomplished in certain situations by transfusing only one RBC unit.

2. FFP use is not optimal in Finland. A large amount of FFP is transfused without the guidance of coagulation tests. This suggests the use of FFP as volume replacement, a practice not recommended by current guidelines.

3. Even though the length of hospitalization for anemic parturients is longer than normal, transfusion of 1 to 2 units of RBCs to a mildly anemic (Hb value between 70 and 100 g/l), healthy parturient does not shorten her hospitalization. This finding supports the current RBC transfusion policy.

4. Although only about 1% of surgical patients receive PLTs, patients undergoing gastric and heart surgery are two of the largest groups of PLT receivers. These patient groups are good targets for PLT use-optimizing efforts.

5. In surgical patients, preoperative morbidity as estimated from the ASA grade assigned correlates with their transfusion requirement. This correlation is more evident in single hospitals than in the combined Finnish data. This information may be useful in optimizing blood order practices.

YHTEENVETO JA JOHTOPÄÄTÖKSET

Aikaisemmissa tutkimuksissa, myös Suomessa tehdyissä, on todettu moninkertaisia eroja verivalmisteiden käytössä samanlaisilla potilasryhmillä. Löydös viittaa siihen, että verensiirtokäytännöt eivät ole kaikkialla optimaalisia. Suomalaisten sairaaloiden tietojärjestelmissä on talletettuna paljon tietoa verensiirroista ja niiden saajista. Tämän tutkimuksen tarkoituksena oli luoda jatkuva, sairaaloiden eri tietojärjestelmiä hyväkseen käyttävä tietojenkeräysjärjestelmä, jolla suomalaisia verensiirtokäytäntöjä voitaisiin seurata ja tutkia.

Tutkimukseen osallistui yhteensä 10 suomalaista sairaanhoitopiiriä (5 yliopisto- ja 5 keskussairaalajohtoista sairaanhoitopiiriä). Tiedot kerättiin vuosien 2002-2005 välillä. Tietovarastoon kerättiin tietoja verivalmisteiden käytöstä sairaaloiden potilashallintojärjestelmistä, verikeskusjärjestelmistä, laboratoriojärjestelmistä ja toimenpidetietojärjestelmistä. Tietojärjestelmien tiedot yhdistettiin tietovarastoon sairaalahoitojaksoiksi tunnistamattomaksi koodatun henkilötunnuksen avulla.

Tietovaraston laadunvarmistuksella todettiin kerätyn tiedon laadun riittävän vertailutarkoitukseen. Laadunvarmennuksessa 96.8% sairaanhoitopiireissä käytetyistä aikuisten verivalmisteista yhdistyi toimittajan, Suomen Punaisen Ristin Veripalvelun, myyntitietoihin. Sairaaloiden välillä todettiin edelleen vaihtelua verensiirtojen määrissä ja verivalmisteita saaneiden potilaiden osuuksissa leikkauspotilailla. Esimerkiksi punasoluja saaneiden polviproteesileikkauspotilaiden osuus vaihteli 12% ja 57% välillä sairaalasta riippuen. Verivalmisteita saaneet potilaat olivat tavallisesti iäkkäitä; yli 50% verivalmisteista annettiin yli 65-vuotiaille. Tavallisin verta saanut potilas oli yli 65-vuotias nainen, jolle oli annettu 2 yksikköä punasoluja. N.10% verivalmisteita saaneista oli lapsia. Punasoluja ja jääplasmaa annosteltiin yleensä kahden yksikön erissä. Yli 60% käytetystä jääplasmasta siirrettiin kirurgisille potilaille, joista noin 25% annettiin sydän- ja verisuonileikkausten yhteydessä. Hyytymistekijätutkimuksia ei tehty kaikkien jääplasmasiirtojen yhteydessä, jopa kolmasosa käytetystä jääplasmasta annettiin ilman tietoa hyytymistekijäpitoisuuksista. Suomessa käytettiin n. 400 punasolu- ja n. 100 jääplasmayksikköä per 1 000 leikkaushoitojaksoa. Lievästi aneemisilla synnyttäjillä 0-2 yksikön punasolusiirto ei vaikuttanut sairaalahoitojakson pituuteen. Aneemisten äitien sairaalahoidon pituus oli kuitenkin keskimääräistä huomattavasti pidempi (5.2 päivää verrattuna keskimääräisen synnyttäjän 3.5 päivää) verensiirrosta riippumatta. Suurin osa verihiutaleista (43%) annettiin veritautipotilaille. Vain 1% leikkauspotilaista sai verihiutaleita. Kuitenkin yli puolet (54%) verihiutaleita saaneista potilaista oli kirurgisesti hoidettuja. Verihiutaleita saavien leikkauspotilaiden sairaalakuolleisuus oli korkea: leikkausten yhteydessä verihiutaleita saaneista potilaista menehtyi sairaalahoitojakson aikana 13.1%,

kun taas kaikista verihiutaleita saaneista menehtyi vain 9.5%. Leikkauspotilailla perussairauksien puolesta sairaimmat saivat eniten verivalmisteita leikkausten yhteydessä. Esimerkiksi ASA 3 ja 4 luokan potilaille (sairaimmaksi luokitellut potilaat) annettiin lähes 70% leikkausten yhteydessä käytetyistä verivalmisteista. Tätä tietoa voitiin käyttää arvioitaessa lonkkaproteesileikkaus-potilaan verivalmisteiden tarvetta ennen leikkausta.

Verivalmisteiden käyttö Suomessa ei ole aina optimaalista. Verensiirtokäytännöt vaihtelevat edelleen merkittävästi leikkauspotilailla terveydenhuollon eri yksiköiden välillä ja lisäksi punasolujen siirto kahden yksikön erissä on kyseenalaista. Usein tapahtuva jääplasman siirto ilman hyytymistekijä-tutkimuksia ei ole nykyohjeiden mukaista. Lievästi aneemisilla, mutta muuten terveillä synnyttäjillä 1-2 yksikön punasolusiirto ei lyhentänyt heidän muutenkin normaalia pidempää sairaalahoitoaikaansa. Nämä potilaat voisivat hyötyä punasolusiirroista pidättäytymisestä. Verihiutaleiden käytön optimointi tulisi suunnata sellaisiin potilasryhmiin, joille verihiutaleita siirretään paljon, kuten veritautipotilaat, sekä gastrokirurgiset ja sydänkirurgiset potilaat. Kaiken-kaikkiaan verivalmisteita siirretään usein perussairaille potilaille.

Tutkimuksessa saatua tietoa verensiirron saajista, hoitokäytäntöjen eroista sekä niiden vaikutuksista voidaan käyttää hyväksi verensiirtokäytäntöjä optimoitaessa.

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APPENDIX

Details of previous studies on blood transfusion epidemiology.

1. Appendix 1

Transfused blood components by medical specialty. ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	SURGICAL INDICATIONS (%)	MEDICAL INDICATIONS (%)
RED BLOOD CELLS				
Friedman BA et. al, 1980 and 1982 (also includes units of whole blood, patients with maximum of 9 units of RBC and maximum of 99 units of red blood cells and whole blood included)	177,398	52,065	61.7% of patients, 63.9% of units	38.3% of patients, 36.1% of units
Cook SS and Epps J, 1991	10,506	2,503	65.6% of patients, 70.9% of units	34.4% of patients, 29.1% of units
Vamvakas EC and Taswell HF, 1994 (includes preoperatively donated RBCs and RBCs salvaged during surgery)	ND	ND	55% of patients, 59% of units	45% of patients, 41% of units
Chiavetta JA et al., 1996	101,116	26,611	55.9% of discharges, 71.9% of units	44.1% of discharges, 28.1% of units
Ghali WA et al., 1994 (includes 1 unit of autologous blood and 169 units of allogenic red blood cells)	170	47	68.8% of units	31.2% of units
Beguin C et al., 1998 (includes allogenic red blood cells, whole blood and autologous blood)	346,115	ND	37% of units	33% of units
Stanworth SJ et al., 2002	594,810	ND	51.2% of units	36.0% of units
Wells AW et al., 2002 (includes allogeneic and autologous RBCs)	9,774	ND	40.7% of units	51.6% of units
Wallis JP et al., 2006	9,003	ND	33% of units	62% of units
Barr PJ et al., 2010	3,804	1,474	29% of patients, 29% of units	71% of patients, 71% of units
FRESH FROZEN PLASMA				
Cook SS and Epps J, 1991	3,303	589	75.9% of patients, 67.4% of units	24.1% of patients, 32.6% of units
Iorio A et.al., 2008	615	109	51.4% of patients	22,9% of patients
PLATELETS				
Cook SS and Epps J, 1991	4,904	236	59.7% of patients, 51.9% of units	40.3% of patients, 48.1% of units
Beguin C et al., 1998	197,226	ND	6% of units	43% of units
BLOOD COMPONENTS COMBINED				
Whyte GS, 1988	1,385 (RBC, FFP, PLT)	367	51.0% of patients	21.3% of patients
Vamvakas EC and Goldsten R, 2002	ND (RBC, FFP, PLT, cryoprecipitate and granulocytes combined)	695	54.8% of patients	45.2% of patients
Tynell E et al., 2001	10,550 (61%RBC, 26% FFP, 13% PLT)	1,904 transfusion episode, which represents transfused patients in one calendar month	47% of patients, 39% of units	29% of patients, 34% of units
Mathoulin-Pelissier S et al., 2000 (includes allogeneic units of RBCs, PLTs and FFP, and preoperative autologous blood donations of RBCs or FFP)	RBC 7,251 FFP 1,127 PTL pooled 120 PTL apheresis 301	3,206	47.2% of ward patients	52.8% of ward patients
Titlestad K et al., 2001	RBC 59,235, FFP 14,894, PLT 7,894	43,698	57% of units	43% of units

2. Appendix 2

Transfused blood components by age. ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	CHILDREN (%)	PATIENTS OVER 65-YEARS OF AGE (%)
RED BLOOD CELLS				
Zimmermann R et al., 1998 (all study patients were younger than 18 years)	2,869	847	<1 years: 30.9% of units,1-5 years: 33.9% of units, 6-10 years: 9.2% of units, 11-17 years: 26.1% of units	
Borkent-Raven BA et al., 2010	1,720,075	ND	3.6% of units <16-years of age	57.6% of units
Wells AW et al., 2002 (includes allogeneic and autologous RBCs)	9,774	ND	2.6% of units to patients under age 16	57.2 of units
Cobain TJ et al., 2007 (English data)	14,794	ND	1.9% of units to patients under age 9	67.2% units to patients over age 60
Cobain TJ et al., 2007 (Australian data)	50,605	ND	ND	47.9% of units to patients over age 70
Wells AW et al., 2009		9,142	4% of patients, 50% of transfused chidren were aged <1 year	
Cobain TJ et al., 2007 (Denmarks' data)	25,553	ND	0.7% of units to patients under age 9	73.6% of units to patients over age 60
Barr PJ et al., 2010	3,804	1,474		68% of recipients were aged 60 or over
Bosch MA et al., 2011 (includes autologous and whole blood units)	19,148	7,384		half of the RBC units transfused to patients aged over 70 and >80 received ¼ of all RBCs
FRESH FROZEN PLASMA				
Zimmermann R et al., 1998 (all patients were younger than 18 years)	1,095	237	<1 years: 28.4% of units, 1-5 years: 37.5% of units, 6-10 years: 8.8% of units, 11-17 years: 25.4% of units	
Borkent-Raven BA et al., 2010	443,697	ND	6,8% of units age <16	41.4% of units
Cobain TJ et al., 2007 (Australian data)	9,642	ND	ND	34.1% of units to patients over age 70
Wells AW et al., 2009	ND	4,232	9% of patients	
Cobain TJ et al., 2007 (Danish data)	2,440	ND	0.3% of units to patients under age 9	65.4% of units to patients over age 60
Cobain TJ et al., 2007 (English data)	1,326	ND	3.1% of units to patients under age 9	66.6% of units to patients over age 60
Iorio A et.al., 2008	615	109		
Mirzamani N et al., 2009	1592	346	2.7% of transfusion episodes were in children under 16	
Stanworth SJ et al., 2011	ND	4,969	6.7% of patients under 16	

Transfused blood components by age (continued). ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	CHILDREN (%)	PATIENTS OVER 65-YEARS OF AGE (%)
PLATELETS				
Cobain TJ et al., 2007 (English data)	2,473	ND	11.6% of units to patients under 9	30.3% of units to patients over age 60
Zimmermann R et al., 1998 (all patients were younger than 18 years)	1,028	163	<1 years: 9.9% of units, 1-5 years: 30.5% of units, 6-10 years: 11.4% of units, 11-17 years: 48.2% of units	
Borkent-Raven BA et al., 2010	241,24	ND	14.6% of units aged <16	29% of units
Cobain TJ et al., 2007 (Australian data)	whole blood 2,734, apheresis 5050	ND	ND	26.1% of units to patients over age 70
Wells AW et al., 2009	ND	3,584	13% of patients	
Cobain TJ et al., 2007 (Danish data)	2,211	ND	4.0% of transfused units to patients under age 9	51.2% of units to patients over age 60
Greeno E et al., 2007	7,401	503	6% of patients under age 8	
BLOOD COMPONENTS COMBINED				
Kamper-Jørgensen M et al., 2009	RBC 2,813,929 FFP 691,797 PLT 270,370 other 5,701	471,951	3.5% of units and 2.6% of recipients (aged 1-19)	70.2% of units and 75.2% of recipients (>60)
Mathoulin-Pelissier S et al., 2000 (includes allogeneic units of RBCs, PLTs and FFP, and preoperative autologous blood donations of RBCs or FFP)	RBC 7,251 FFP 1,127 PTL pooled 120 PTL apheresis 301	3,206	ND	56.6% of patients
Titlestad K et al., 2002	RBC 59,235, FFP 14,894, PLT 7,894	43,698	ND	ND
Currie CJ et al., 2004	ND (RBC, FFP and PLT combined)	2,801	ND	46% of blood was transfused to patients over age 70
Tynell E et al., 2005	ND (RBC, FFP and PLT combined)	990	ND	64% of patients
Kamper-Jørgensen M et al., 2009	RBC 901,291 FFP 139,691 PLT 62,038 other 2,061	135,038	3.3% of units and 3.1% of recipients (aged 1-19)	66.3% of units and 72.8% of recipients (>60)
Bosch MA et al., 2011	RBC 19,148 FFP 3,070 PLT 1,812	8,019	5.4% of patients were under age 15	

3. Appendix 3

Transfused blood components by gender. ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	MALE PATIENTS (%)
RED BLOOD CELLS			
Vamvakas EC and Taswell HF, 1994; Cobain TJ et al., 2007, US data (includes preoperatively donated RBCs and RBCs salvaged intraoperatively)	ND	ND	48.5% of units, 45.3% of patients
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	28,440	6,590 (includes all RBC, FFP and PLT transfused patients)	60.0% of units
Zimmermann R et al., 1998 (all patients aged <18)	2,869	847	59.2% of units
Borkent-Raven BA et al., 2010	1,720,075	ND	50% of units
Wells AW et al., 2002 (includes allogeneic and autologous RBCs)	9,537	ND	50.7 of units
Cobain TJ et al., 2007 (England data)	14,794	ND	50.4% of units
Anderson SA et al., 2007 (includes only patients age ?65 and includes both RBC and whole blood units)	61,278	15,579 inpatient stays	41.6% of inpatient Medicare stays
Menis M et al., 2009 (includes only ambulatory patients >65 and includes both RBC and whole blood units)	16,119	10,705 outpatient claims	42.8% of outpatients claims
Cobain TJ et al., 2007 (Australian data)	50,605	ND	52.5% of units
Wells AW et al. 2009	ND	9,142	44% of patients
Cobain TJ et al., 2007 (Danish data)	25,553	11,016	52.7% of units
Barr PJ et al., 2010	3,804	1,474	47% of patients, 48% of units
Madsen et al., 2010	25,344	4,427	8.6/1,000 (one-year period prevalence rate), age-corrected number 6.8/1,000
Bosch MA et al., 2011 (includes autologous and whole blood units)	19,148	7,384	54.5% of units
FRESH FROZEN PLASMA			
Vamvakas EC and Taswell HF, 1994; Cobain TJ et al., 2007 (US data)	ND	ND	55.1% of units, 51.2% of patients
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	8,592	6,590 (includes all RBC, FFP and PLT transfused patients)	59.8% of units
Zimmermann R et al., 1998 (all patients were younger than 18)	1,095	237	59.6% of units
Borkent-Raven BA et al., 2010	443,697	ND	59% of units
Cobain TJ et al., 2007 (Australian data)	9,642	ND	57.3% of units, 57.3% of patients
Wells AW et al. 2009	ND	4,232	57% of patients
Cobain TJ et al., 2007 (Danish data)	2,440	ND	63.3% of admissions
Cobain TJ et al., 2007(English data)	1,326	ND	59.6% of units
Iorio A et.al., 2008	615	109	68.8% of patients
Mirzamani N et al., 2009	1592	346	63.5 % of transfusion episodes
Bosch MA et al., 2011	3,070	715	61.2% of units

Transfused blood components by gender (continued). ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	MALE PATIENTS (%)
PLATELETS			
Vamvakas EC and Taswell HF, 1994; Cobain TJ et al., 2007 (US data)	ND	ND	57.3% of units, 57.3% of patients
Cobain TJ et al., 2007(English data)	2,473	ND	66.0% of units
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	2,704	6,590 (includes all RBC, FFP, and PLT transfused patients)	63.1% of units
Zimmermann R et al., 1998 (all patients were younger than 18)	1,028	163	62.5% of units
Borkent-Raven BA et al., 2010	241,24	ND	60% of units
Cobain TJ et al., 2007 (Australian data)	whole blood 2,734, apheresis 5050	ND	62.4% of units
Wells AW et al. 2009	ND	3,584	58% of patients
Cobain TJ et al., 2007 (Danish data)	2,211	ND	62.4% of admissions
Bosch MA et al., 2011 (dose= 5-unit pool or equivalent plateletpheresis unit of PLTs)	1,812	981	59% of doses
BLOOD COMPONENTS COMBINED			
Vamvakas EC and Goldsten R, 2002	ND (RBC, FFP,PLT, cryoprecipitate and granulocytes combined)	695	60.1% of patients
Tynell E et al., 2001	10,550 (61%RBC, 26% FFP, 13% PLT)	1,904	44% of patients
Kamper-Jørgensen et al., 2009	RBC 2,813,929 FFP 691,797 PLT 270,370 other 5,701	471,951	52.9% of units; 43.6% of patients
Tynell E et al., 2005	ND (RBC, FFP, and PLT combined)	1,922	46% of patients
Mathoulin-Pelissier S et al., 2000 (includes allogeneic and autologous blood components)	RBC 7,251 FFP 1,127 PTL pooled 120 PTL apheresis 301	3,206	49.9% of patients
Titlestad K et al., 2002	RBC 59,235, FFP 14,894, PLT 7,894	43,698	47% of admissions
Kamper-Jørgensen et al., 2009	RBC 901,291 FFP 139,691 PLT 62,038 other 2,061	135,038	53.2% of units; 44.6% of patients

4. Appendix 4

Transfused blood components by diagnostic groups. ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	DIAGNOSTIC GROUP	NUMBER OF UNITS OR PATIENTS
RED BLOOD CELLS				
Chiavetta JA et al., 1996	101,116	26,611	1. Neoplasms 2. Digestive system 3.Circulatory system	26.7% of units 17.9% of units 16.2% of units
			1. Blood and blood-forming organs 2. Neoplasms 3. Injury and poisoning	43.9% of patients 16.6% of patients 10.9% of patients
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	28,440	6,590 (includes all RBC, FFP and PLT-transfused patients)	1. Nonhematologic neoplasms 2. Circulatory system 3. Digestive system	26.76% of units 22.93% of units 11.43% of units
Zimmermann R et al., 1998 (all study patients were younger than 18)	2,869	847	1. Congenital nonvalvular heart defects 2. Lymphatic leukemia 3. Premature birth	18.96% of units 8.92% of units 7.88% of units
Lim YA et al., 2004	171,916	ND	1. Neoplasms 2. Injury and poisoning 2. Digestive system	28.2% of units 19.6% of units 12.9% of units
Borkent-Raven BA et al., 2010	1,720,075	ND	1. Neoplasms 2. Circulatory system 3. Injury and poisoning	22.2% of units 21.5% of units 10.5% of units
Mathoulin-Pelissier S et al., 2000 (includes allogeneic units of RBCs and preoperative autologous blood donations of RBCs)	7,251	2,701	1. Neoplasms 2. Injury and poisoning 3. Digestive system	42% of units 16% of units 14% of units
Wells AW et al. 2009	ND	9,142	1. Digestive group 2. Musculoskeletal group 3. Hematology group	19 % of patients 15 % of patients 13 % of patients
Cobain TJ et al., 2007 (Danish data)	25,553	11,016	1. Neoplasms 2. Digestive system 3. Circulatory system	25.7% of units 15.5% of units 14.5% of units
Barr PJ et al., 2010	3,804	1,474	1. Gastrointestinal conditions 2. Cardiac conditions 3. Cancer	45% of patients 39% of patients 38% of patients
Madsen et al., 2010	25,344	4,427	1. Neoplasms 2. Diseases of the circulatory system 3. Diseases of the digestive system	2/1,000 (one-year period prevalence rate) 1.4/1,000 (one-year period prevalence rate) 1.3/1,000 (one-year period prevalence rate)
Bosch MA et al., 2011 (includes autologous and whole blood units)	19,148	7,384	1. Blood and blood-forming organs 2. Neoplasms 3.Circulatory system	22.4% of units 17.4% of units 10.6% of units
FRESH FROZEN PLASMA				
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	8,592	6,590 (includes all RBC, FFP and PLT-transfused patients)	1. Nonhematologic neoplasms 2. Digestive system 3. Circulatory system	25.36% of units 21.73% of units 17.07% of units
Zimmermann R et al., 1998 (all study patients under age 18)	1,095	237	1. Congenital nonvalvular heart defects 2. Congenital valvular heart defects 3. Congenital cardiovascular malformations	15.53 of units 8.58 of units 6.30 of units
Lim YA et al., 2004	69,301	ND	1. Neoplasms 2. Digestive system 2. Injury and poisoning	31.6% of units 22.5% of units 16.8% of units
Borkent-Raven BA et al., 2010	443,697	ND	1. Circulatory system 2. Neoplasms 3. Injury and poisoning	47.8% of units 12.7% of units 9.4% of units
Mathoulin-Pelissier S et al., 2000 (FFP and preoperative autologous blood donations of FFP)	1,127	327	1. Injury and poisoning 2. Digestive system 3. Neoplasms	29% of units 23% of units 14% of units
Wells AW et al. 2009	ND	4,232	1. Digestive group 2. Hepatobiliary group 3. Cardiac group	21 % of patients 15 % of patients 12 % of patients
Cobain TJ et al., 2007 (Danish data)	2,440	1,980	1. Circulatory system 2. Digestive system 3. Neoplasms	39.2% of units 20.5% of units 10.4% of units
Mirzamani N et al., 2009	1592	346	1. Gastrointestinal bleeding 2. Trauma 3. Neoplasm	25% of units 14% of units 14% of units
Bosch MA et al., 2011	3,070	715	1. Digestive system 2. Blood and blood-forming organs 3. Circulatory system	24.3% of units 16.0% of units 15.3% of units

Transfused blood components by diagnostic groups (continued). ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	DIAGNOSTIC GROUP	NUMBER OF UNITS OR PATIENTS
PLATELETS				
Lim YA et al., 2004	156,272	ND	1. Neoplasms 2. Digestive system 3. Blood and blood-forming organs	53.5% of units 10.5% of units 8.7% of units
Borkent-Raven BA et al., 2010	241,24	ND	1. Neoplasms 2. Circulatory system 2. Blood and blood-forming organs	41.2% of units 21.0% of units 8.7% of units
Mathoulin-Pelissier S et al., 2000	PTL pooled 120, PTL apheresis 301	402	1. Neoplasms 2. Blood and blood-forming organs and 3. Injury and poisoning	76% of units 6% of units 6% of units
Zimmermann R et al., 1997 (includes allogeneic and autologous blood components)	2,704	6,590 (includes all RBC, FFP and PLT-transfused	1. Leukemia or lymhoma 2. Nonhematologic neoplasms 3. Digestive system	38.09% of units 19.12% of units 11.54% of units
Wells AW et al. 2009	ND	3,584	1. Hematology group 2. Cardiac group 3. Pediatric group	27 % of patients 17 % of patients 13 % of patients
Cobain TJ et al., 2007 (Danish data)	2,211	1,475	1. Neoplasms 2. Circulatory system 3. Blood and blood-forming organs	66.2% of units 16.2% of units 4.9% of units
Quareshi H. et al., 2007	ND	4,421	1. Hematology patients 2. ICU patients 3. Cardiac surgery patients	48% of patients 21% of patients 8% of patients
Greeno E et al., 2007	7,401	503	1. Cancer of hematologic disease 2. Cardiovascular disease 3. Gastrointestinal disease	56% of patients 22% of patients 8% of patients
Bosch MA et al., 2011 (dose= 5-unit pool or equivalent plateletpheresis unit of PLTs)	1,812	981	1. Blood and blood-forming organs 2. Neoplasms 2. Circulatory system	63.0% of doses 10.0% of doses 6.2% of doses
BLOOD COMPONENTS COMBINED				
Tynell E et al., 2005	ND (RBC, FFP, and PLT)	990	1. Tumors 2. Circulatory system 3. Musculoskeletal and connective tissue system	1993: 26% of patients; 2000: 24% 1993: 23% of patients; 2000: 19% 1993: 13% of patients; 2000: 14%

5. Appendix 5

Transfusions recipients' most frequent single ICD-diagnoses.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	MOST FREQUENT ICD-DIAGNOSES
RED BLOOD CELLS			
Chiavetta JA et al., 1996	101,116	26,611	Gastric, duodenal ulcer, and gastrointestinal hemorrhage, chronic ischemic heart disease, malignant neoplasm of colon, rectum, and anus
Titlestad K et al., 2001	59,235	43,698 (all RBC, FFP and PLT-transfused patients)	Hospital A: Atherosclerotic heart disease, abdominal aortic aneurysm, ruptured, malignant neoplasm of breast Hospital B: Angina pectoris, unspecified, unstable angina, malignant neoplasm of bladder, unspesified
Anderson SA et al., 2007 (includes only inpatients age >65 and includes both RBC and whole-blood units)	61,278	15,579 inpatient stays	Other forms of chronic ischemic heart disease, acute myocardial infaction, fracture of neck of femur
Menis M et al., 2009 (includes only ambulatory patients age >65 and includes both RBC and whole-blood units)	16,119	10,705 outpatient claims	Anemia, unspecified, neoplasm of uncertain behavior of other and unspecified sites and tissues (other lymhatic and hematopoetic tissues), anemia in neoplastic disease (chronic)
Bosch MA et al., 2011 (includes autologous and whole-blood units)	19,148	7,384	GI hemorrhage, myelodysplastic syndromes, reduction and/or fixation of fracture of femur
FRESH FROZEN PLASMA			
Titlestad K et al., 2001	14,894	43,698 (all RBC, FFP and PLT transfused patients)	Hospital A: Atherosclerotic heart disease, abdominal aortic aneurysm, ruptured, abdominal aortic aneurysm, without mention of rupture Hospital B: Angina pectoris, unspecified, unstable angina, aortic valve stenosis
Bosch MA et al., 2011	3,070	715	Plasma pheresis, therapeutic, operations on valves and septa of heart, liver transplant
PLATELETS			
Titlestad K et al., 2001	7,894	43,698 (all RBC, FFP and PLT transfused patients)	Hospital A: Subacute myeloid leukemia, acute myeloid leukemia, acute promyelocytic leukemia Hospital B: Angina pectoris, unspecified, unstable angina, acute myeloid leukemia
Bosch MA et al., 2011 (dose= 5-unit pool or equivalent plateletpheresis unit of PLTs)	1,812	981	Acute leukemia, marrow or hematopoietic stem cell transplant, aplastic anemia
BLOOD COMPONENTS COMBINED			
Lim YA et al., 2004	RBC 171,916, FFP 69,301, PLT 156,272	31,308	Acute myeloid leukemia, liver cell carcinoma, other and unspecified cirrhosis of liver

6. Appendix 6

Transfusion recipients' most common surgical procedures. ND=no data.

RERERENCE	NUMBER OF TRANSFUSED UNITS	NUMBER OF TRANSFUSED PATIENTS	COMMON SURGICAL INDICATIONS
RED BLOOD CELLS			
Stanworth SJ et al., 2002	610,676	ND	General surgery: 13.62 % of units; orthopedic surgery: 10.17% of units; cardiothoracic surgery: 8.14% of units Digestive system: 20.1% of units; cardiovascular system: 15.8% of units; diagnostic and therapeutic procedures: 15.2% of units (category includes blood transfusion i.e. exchange transfusion as primary diagnosis)
Chiavetta JA et al., 1996	101,116	26,611	1. Total hip replacement: 3.8% of transfused units 2. Bypass anastomosis:3.8% of transfused units 3. Open reduction of fracture: 3.7% of transfused ur
Wells AW et al., 2002 (includes allogeneic and autologous RBCs)	9,537	ND	1. Total hip replacement: 4.6% of units 2. Abdominal surgery (excluding colorectal): 4.4% o 3. Coronary artery bypass grafting: 4.1% of units
Anderson SA et al., 2007 (includes only patients age >65 and includes both RBC and whole blood units)	61,278	15,579 inpatient stays	1. Bypass anastomosis for heart revascularization: 9.1% of units 2. Diagnostic procedures on small intestine: 7.2% of units 3. Joint replacement of lower extremity: 6.8% of units
BLOOD COMPONENTS COMBINED			
Tynell E et al., 2005	ND (RBC, FFP and PLT)	990	1. Coronary heart surgery: 1993 16% of operations with transfusion; 2000 14% 2. Hip replacement: 1993 12% of operations with transfusion; 2000 18% 3. Surgery for femoral fracture: 1993 7% of operations with transfusion; 2000 11%